THE GENERAL INDICATIONS FOR PSYCHOLOGICAL TREATMENT *

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THE decision as to whether a patient is likely to benefit from detailed psychological treatment, with the choice of the technique most likely to succeed, is a severely practical matter. Psychotherapy misapplied can be both uneconomic and harmful. Any method used must, therefore, be considered with strict reference to the central aim, which is to remedy, in the individual under review, the unhappiness and inefficiency, both personal and social, which are the products of his psychological maladjustment. If the subject of a psychoneurosis proves on investigation to have made an inept use of his resources and potentialities, the hope is that he may be assisted by psychotherapy to reorganise his mental economy in the interests of greater efficiency.

The social structure with which so many patients are at odds owes its complexity to the development in man of the means whereby previous sensory experience can be recalled and thought about in the absence of the original stimulus, and of the development within society of the means of communication, so that one person can be influenced by the ideas of another, conveyed through the symbols of language. When planning psychotherapy it should be borne in mind that the language in which the effects of experience are recorded on the tablets of the developing brain—the language of perception and of the unique inner world of the self—is not the same as the language which human beings use to communicate with one another. When we try to understand or to influence another self by means of ideas, we are continually held up by the need to reformulate and translate the subjective language of recall, of feeling and of impulse into the less adequate language of words. It is this process of translation more than any other factor that has divided psychotherapy into schools, each with its own interpretations of the same processes. In this respect they resemble the inhabitants of different countries, living similar lives and with similar aims, yet not always able to develop the finer points of mutual understanding and sympathy through lack of a common language. Since most of the controversies between schools of psychopathology are largely a matter of language, it is therefore important that, so far as is possible, psychiatrists should speak in the Esperanto of psychopathology—that is, in Plain Words, unambiguous in meaning to specialist and layman alike.

It is possible, though uncommon, for one person, who is present at the right time and who utters a few words only, to alter the whole course of the thoughts and behaviour of another, who from that moment is able to bring about his own readjustment. To find such words and the occasion for their use is an ideal of psychotherapeutic achievement. It is, unfortunately, an ideal almost beyond attainment. Yet how often, when we have been rewarded with some almost comparable experience, have we been at a loss to know quite how or why it happened unless, of course, by means of what Henry Maudsley (1886) called "a subtle collusion with the self", which we now would call rationalisation, we can turn our wonder into triumph.

We have to confess that in psychotherapy chance plays no small part and that we are at times manipulating and releasing forces which we do not fully understand. In psychopathology, too, attempts are made to describe these forces in terms of systems of reference which are as purely theoretical as the cosmic explanations of the ancients. Just as the alchemists of old described the reactions of chemical substances in terms of the movements of the heavenly bodies, so the psychopathologist today may be tempted to forget the extent of our ignorance, evade the effort of abstract thought, and take the easy path of the allegorical description of mental life. It is tempting to accept literally one or other of the dangerously oversymbolised and oversimplified visual diagrams or blueprints of the mind which are available. Celestial or genital, the symbols serve the same purpose of evading the unknown and they serve, too, to confuse the uninitiated. Fortunately, just as chemistry was applied for the benefit of man even when its theoretical dynamics centred on the fallacious Phlogiston theory, so the benefits of our observation of people's psychological responses to ideas and stresses can be turned to practical account, even with a questionable theoretical basis, until science catches up. Hypotheses and theories may be very valuable, provided that they never assume the status of beliefs. As Appleton (1953) has said, a theory is only an hypothesis that has become respectable. No-one has put this better than Sigmund Freud (1949), who was well aware of the purely empirical purpose of his constructs:

> "The future may teach us how to exercise a direct influence, by means of particular chemical substances, upon the amounts of energy and their distribution in the apparatus of the mind. It may be that there are other undreamt-of possibilities of therapy. But for the moment we have nothing better at our disposal than the technique of psycho-analysis, and for that reason, in spite of its limitations, it is not to be despised."

If we put "psychotherapy as we now understand it" in place of "the technique of psychoanalysis", Freud's statement of the position can give no better picture of the caretaker function of psychopathology at the present day. We are likely to have the caretaker with us for a long time. For even if it were possible to understand in detail the functioning of so complicated a machine as the brain, it would take a greater brain than ours to encompass its total working in one individual at one moment of time. There must, therefore, be a long future for hypotheses and symbolic language with their function of enabling us to extend the reach of our abstract understanding in the same way as the symbols of mathematics take us beyond the range of present observation in the field of pure science. Psychopathology is as legitimate a servant of the psychotherapist as mathematics is of the physicist, but a servant who must never be allowed to assume the mastery.

The Place of Psychotherapy

Health is defined in the Constitution of the World Health Organisation as "a state of complete physical,

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mental and social well-being" and this definition is defended on the score that the representatives of sixty-four governments, like the three million mothers, cannot be wrong. If mental adjustment to this puristic standard of dull serenity is to be the aim of mental hygiene, it is difficult to see how psychotherapy, which is one of the most expensive forms of treatment in terms of human time and effort, can ever help us much. For the moment, a simple statement of our aims in treating the individual is that we should try and deal with his maladjustment where it causes distress to himself or to those who would live in harmony with him, and to give him help until he reaches a point where he can help himself. He must then learn how to live in such a way as to avoid strains with which he is inadequate to deal. Physical, social and psychological treatment must thus go hand in hand, with the emphasis placed on that which is most likely to be successful. We can be encouraged by the fact that our efforts will be supported by protective and compensatory mental mechanisms comparable in purpose to the homœostatic mechanisms involved in the physical defences of the organism. These mechanisms have been well tried and proved in the fire of natural selection. It is encouraging to remember that before the advent in medicine of specific therapies, the basis of practice was to support the natural resistance and healing forces of the body. The principles of expectant treatment so ably laid down by John Hilton (1863) nearly a hundred years ago are still well worth the attention of the psychotherapist, who would be powerless were it not for the innate recuperative qualities of the human psyche. Nowhere is this better seen than in psychotherapy with children who, one is tempted to think, are sometimes able to recover even in the teeth of intensive psychotherapy.

In some respects psychological treatment can be compared to the medical assistance which is given in childbirth—an assistance which has also become more necessary with the advance of civilisation. The fact that pregnancy must come to an end somehow is as inevitable as the fact that the maladjusted patient, as opposed to the psychotic, must after treatment continue to live in a similar world to that in which his troubles began. The need in childbirth is to encourage the mother to make the best use of her own natural resources, to be able to give the right help at the right time and to reduce the incidence of complications by not interfering too much. These are exactly the rules we might follow with advantage in planning psychological treatment. The psychoneuroses can be looked upon as exaggerations and distortions of normal protective mental mechanisms (Kennedy 1940). In treating them our aim will always be to find the way back to a life of reasonable harmony unless serious constitutional defect or disorder of the total personality makes it necessary to lower our sights and accept an invalid adaptation.

The Diagnostic Interview

The first contact which a psychoneurotic patient makes with someone who will listen to him and who shows interest and sympathy is the starting-point of a therapeutic relationship. The therapeutic value of the initial consultation may be very great, especially when the doctor is the first person who has conveyed to the patient by his inquiries that the illness is not unique, that it can be understood by someone else, and that it is not a matter for self-reproach. As an impression is built up of the causes of the maladjustment, of the constitutional assets of the patient, his deficiencies, and the effects upon him of stresses arising from within and without, therapeutic opportunities occur which may be difficult to reconstruct later.

That the patient should be treated throughout by the doctor to whom he has first brought his troubles is an ideal state of affairs. It is hoped that it will be realised more often when the medical student is taught as much about human beings as about their diseases and can be relied upon to give psychological first-aid. More often than not, reference to a specialist is necessary. The latter may undertake treatment himself, or he may see the patient more than once for more detailed investigation before finally making his plan. If he then decides that specialised psychotherapy is necessary this may entail yet one more change of doctor.

In considering the advisability of treatment by a psychotherapist who has the time and skill to carry out one of the longer methods, the consultant has certain definite responsibilities:

1. He must, in giving his opinion, acquaint both general practitioner and therapist with any organic and situational factors which may influence the course of the therapy. In doing so he must try to foresee any crises, such as attempts at suicide, fugues, or explosions of violence. When psychosomatic disorder is present, he must arrange for coincident medical treatment, while if there are potential legal implications in the patient's behaviour the position should be clearly stated before treatment is undertaken. Having thus given his own statement of the balance between consitution and stress and of the prognosis as he sees it, he must then leave the psychotherapist free to interpret the patient's needs in the light of his own inquiries.

2. He must try to foresee in a general way what form of psychotherapy and what sort of psychotherapist is most likely to succeed. Since the different psychotherapeutic approaches are not often specific to the types of disability which the patient may present, and are more related to his personality, there can be no question of prescribing treatment in detail. Quite different approaches can be equally successful in the same sort of case, so that it must be left to the psychotherapist to adapt his own methods to the needs of the patient. The diagnostic physician, therefore, needs to know the interests and special aptitudes of the therapists to whom he refers patients. A skilled hynoptist, for instance, whose therapy is mainly of the imposed kind and who is helped by his firm belief in his own methods, may be excellent for a patient whose capacity for insight is small, or whose symptoms are restricted. On the other hand, a realistic and self-critical patient requires a mature therapist capable of accepting responsibility for dealing with the strong transferences which are often a feature of the integrated physical and psychological treatment of, say, the intelligent depressive.

3. The consultant must try to minimise the effects of the transfer from one physician to another by preparing the patient for his relationship with the therapist. He must not prejudice this by rash promises, or attempt to impress his personality on the patient more than is necessary in the latter's immediate interests. At the end of successful treatment, after the last interview with his psychotherapist, the patient should be saying something like this: "And I'm grateful to that chap at the hospital—I forget his name—who sent me on to you—it seems a long time ago." This aspect of his task involves a good deal of saintliness on the part of the consultant.

Here, perhaps, an opinion may be given as to what should be the successfully treated patient's attitude to his psychotherapist. When he has reached a point where his own mental powers of adjustment are adequate, he will have no further need of the therapist, who should recede quietly from consciousness, his catalytic function accomplished. If they meet in the street, therefore, he might suddenly revive with slight embarrassment a train of thought that

is beginning to become unfamiliar through disuse. " I am always meaning to write you a line but I never get round to it " is perhaps a good sign of a successful issue. It is a little sad that in psychotherapy, which has its share of frustrations and rewards, the doctor must resist the temptation to build a monument to his success, at any rate in the mind of the patient. Effusive gratitude too often carries with it a residuum of dependence.

Since referral to a psychotherapist implies a diagnosis of functional disorder, it is the responsibility of the diagnostic physician to put it to the patient that his symptoms are of psychological origin and to explain, if necessary, what a psychotherapist is. If the idea of treatment is not at first acceptable, it may be possible to persuade the patient at least to try the idea out. No promises should be given. The psychotherapist will be presented more often as someone " who will help you to sort out your ideas and to find out what is the matter so that you can put it right " rather than as " someone who will put you right ".

Choice of Method

The question whether psychotherapy is indicated needs a clear and definite answer. Decisions on the kind of treatment, however, can be only approximate, requiring to be modified in the light of continued therapeutic inquiry. The number of variables to be considered in a diagnostic situation of this kind may, in fact, be great enough for the process of considering them to rank as an act of intuition. Psychotherapy, which can be interpreted so differently in different hands, is at least as much art as science and intuition is therefore not out of place. Semi-intuitive, therefore, though the final decision may be, it is greatly helped if in his training the psychiatrist has acquired good habits of mind and has achieved some clarity in his ideas about psychological treatment and its aims. In 1916, before the great expansion of psychotherapy, Adolf Meyer (1951) foresaw this need.

" No field of biology is more in danger of verbosity than ours. Hence let us cultivate principles of economy . . . Nothing will help more towards a systematisation of a generally useful and intelligible body of . . . facts than conscientious habits of cross-reference."

In spite of the dangers inherent in the visual representation of abstract ideas, I shall try to give some idea of the principles on which such a process of cross-reference is based. The different types of psychotherapy can be represented on a scale. Of the several parameters which might be chosen (Kennedy 1960), the one here selected is the extent to which the patient himself solves his problem or to which the solution is imposed upon him by the therapist. It is a scale of relative participation in the real work of treatment by patient and therapist. The word *work* is used because I believe that, if psychotherapy is to be successful, one or both of the parties to it must work very hard. One might put it that, if there are neither tears nor sweat in the course of psychological treatment, someone is wasting his time. On this basis, methods may be divided into:

Imposed therapies.
Reconstructive counselling.
Conditioning and rehabilitation.
Anamnesis and abreaction.
Review and resynthesis.
Personal analysis and reorientation.

The groups chosen are in no way mutually exclusive. For instance, imposed methods may render a patient capable of achieving a sound insight as treatment progresses.

Conditions which may Respond to Psychotherapy

The diagnostic groups cannot be placed in any constant order of amenability, for the possibility of improvement depends as much on the patient's constitution and circumstances as on the category to which his disability can be assigned. Hence, in this paper, the types of illness likely to respond to psychotherapy have been divided into a number of groups labelled according to the clinical features which can be elicited at the initial inquiry. The order in which they are given is based on the extent to which, in my experience, they have responded to psychological treatment. The groups and their order are thus inevitably personal, and modifiable in the light of the experience of others. Probably, however, they are better than no classification at all for they are intended as an aid to the planning of treatment, a mental operation which is not helped by unnecessary vagueness.

I. Acute psychological responses to stress. Panic, terror and short-term escape reactions such as amnesia.

II. Purposive functional disabilities (hysteria) when single and recent in appearance with no previous history of severe neurosis.

III. Acute tension, aggressive and protesting behaviour in childhood and adolescence. Anxiety states of recent origin.

IV. Reactive depression where the constitutional component is relatively small and the stress severe.

V. Inefficient attitudes to the stress of physical illness, to family and social misfortune and to endogenous depression.

VI. Organ neuroses (e.g., effort syndrome, mucous colitis, functional anorexia).

VII. Certain " psychosomatic " disorders including allergic disorders with psychological precipitants but excluding peptic ulcers, hypertension and asthma.

VIII. Failure of adaptation to cerebral deterioration and senile decline.

IX. Disorders of habit; addictions including alcoholism.

X. Obsessions and impulses if single and occurring in early life in sound personalities.

In these ten groups there is some prospect, in declining order, of wholly psychological treatment helping to bring about a satisfactory adaptation to life, in time to prevent permanent dependence. A list of conditions which are partially helped by supportive psychotherapy, or in which psychotherapy plays a minor, if essential, role, would give a very different order. Endogenous depression, for instance, although it may recover spontaneously, is not likely to do so as the result of psychotherapy alone, and physical treatment is indicated once a confident diagnosis has been made. On the other hand, the treatment of depression impersonally by physical means alone may leave the patient bewildered and with no better insight into his vulnerability to mood change than he had at the outset. For this reason psychotherapy is essential in endogenous depression but, since it is subsidiary to physical methods, it is not included.

While there are not many forms of psychiatric disorder in which intensive personal psychotherapy cannot at least comfort, it cannot be available to all, and we have to deploy our efforts where they will do the most good. The economies must necessarily be made by increasing our skill in deciding *which* patients in each group are to be given the opportunity and how much time they are to be given. In patients of poor intelligence or capacity for insight, imposed therapies such as hypnosis or direct suggestion are of most value, and without them it would be difficult to relieve the type of symptom—such as amnesia, aphonia, and mutism—which prevents communication between patient and physician (Kennedy 1940). Such treatment must be available when it is

needed, and should be available for instance in hospital casualty departments (Kennedy and Neville 1957). The effects of leaving symptoms of this kind unrelieved are serious, for with each passing day the patient's escape into invalidism, often tentative at first, becomes confirmed by its success in shielding him from reality. In such cases a general psychiatrist will usually give emergency treatment himself rather than call in a psychotherapist with consequent delay. It is for this reason that the shorter methods, including hypnosis, should be included in the training and part of the armamentarium of *every* psychiatrist. The objection is often raised that purely symptomatic treatment of the imposed kind is usually followed by relapse, because it does not deal with underlying maladjustments and morbid attitudes. This is open to question in that gross hysteria is commoner in constitutionally vulnerable people in the absence of the most severe and acute forms of stress, and such patients are liable to relapse. Even the most intensive psychotherapy will not make them less vulnerable, for their problems are likely to be due to a defect in the physical substrate of mind and are not capable of full solution. On the other hand, there is evidence that short-term treatment may be followed by long periods of relatively good adjustment without a return of symptoms.

The Results of Psychotherapy

Assessment of the results of psychological treatment presents formidable difficulties. That the patient is delighted with the outcome may mean no more than that he has found a respectable way of rationalising an egocentricity which formerly came into conflict with his conscience. It may be that regular psychotherapy over a period of years can give some sort of purpose to a life which was formerly idle and empty. The presence or absence after treatment of symptoms complained of at the initial diagnostic interview is an unambiguous criterion if it is associated with an estimate of the patient's general adjustment to life and work and the absence of signs of gross failure such as delinquency, attempts at suicide, alcoholism or divorce. Except in conditions such as alcoholism where the simple fact that the patient is drinking/not drinking gives a direct measure of success or failure, it is difficult to apply statistics to a matter where the data are so subject to individual interpretation and bias, although the attempt has been made by several authorities (Eysenck 1952). That the use of percentages as a means of expressing a general trend can lead to absurdities in the presence of a bias of this kind is well illustrated by the evidence given to the Royal Commission on Capital Punishment (1949–53) on the results of psychotherapy in delinquents. The only safe conclusion to be drawn from recent studies seems to be that the greatest of psychotherapists, Time, in the form of the waiting-list, is successful in a surprising proportion of cases, and that patients who have attended a private analyst for some time rarely fail to conclude, if they are still attending, that it is worth their while to do so.

The conclusions which follow are personal and are not supported by statistics.

So far as *hysteria* is concerned, even if its causes lie deep, the formation of symptoms can often be prevented. The child who has been off school with a cold and who tries to get an extra day by claiming a headache is using, in a simple but not deliberate manner, a mental mechanism of escape from a civilised obligation, and the doctor who says "Nonsense, up you get" may be reversing a tendency which could be serious if encouraged by an indulgent parent, a "better be on the safe side" doctor, or a frustration-phobic psychiatrist. With hysteria "il n'y a que le premier pas qui coûte". While to the psychoneurotic with a really serious problem who presents it in the form of a conversion symptom, a moral lecture is an unhelpful affront, there are occasions when the evasion is not so unconscious as to be inaccessible to a reminder not to take the easy path. Certainly, in compensation cases, the course of the illness can be materially affected by the fact of who sees the patient first—a downright general practitioner or the compensation secretary of the trade union, hungry for triumphs. At the outset, adoption of the invalid attitude is usually accompanied by a phase of suggestibility which can and should be exploited while it lasts. The importance of the time-factor in early psychoneurosis was well illustrated in time of war, where a few days' delay before treating the acute breakdown made rehabilitation long and difficult. In civilian practice this is seen when the symptom is of the acute generalised kind (e.g., aphonia, mutism, amnesia, or panic state) and an insightful approach quite out of the question. The breaking down of the non-realisation barrier is then a matter of urgency. Among the methods which can be used is hypnosis. As the method which opened the door to the possibilities of psychological treatment, in the hands successively of Charcot, Bernheim, Liebault, Janet, Breuer and Freud, it has the sanction of history. It requires no preparation or apparatus and is therefore ideal for the functional emergency. Admittedly, we do not know how it works, but this applies to a great deal that happens in the therapeutic relationship. The fact that hypnosis has often been used by charlatans may give it a bogus air, but medicine has had to incorporate into its professional practice much that started in the market-place.

Where anxiety is nearer to the surface, cathartic methods will often bring some relief, but in some quarters the idea dies hard that abreaction should be made an object in itself. The main function of abreaction in the course of psychotherapy is to bring new material to the surface so as to allow patient and physician to assess its importance. The relief it brings is rarely permanent if the subsequent work of resynthesis is not taken up. In the case of *obsessional states*, a great deal of the psychotherapy that has been given has probably been wasted, for the long-term results are now known to be poor. The fallacy in treating obsessional states has been the belief that if psychopathological material of great interest and richness keeps appearing at the interviews, with strong abreaction, the patient will necessarily benefit. A common sequence in cases of obsession is that the appearance of symbol-rich material, often elicited with suspicious ease, is followed by great relief for a week or two. Patient and therapist then seek in vain to produce the same effect once more. Months or years after he has been abandoned in despair, the patient may be found to have recovered spontaneously, or the organic state or functional psychosis of which the obsessions were a symptom may have revealed itself.

It is often forgotten that even where *anxiety* is the most prominent feature, there is a major place for psychotherapy in which the place of emotion is secondary to a simple conscious discussion of the patient's immediate problems. Here the patient may be compared with a bankrupt whose business has failed from a combination of bad luck and bad management. He agrees to the

appointment of a receiver who may be able to come in and keep the business going and help him, the proprietor, to get it on its feet. Old problems are seen through new and experienced eyes as the patient helps the therapist to make a detached reconstruction of the situation. Here abreaction is only an incident and extremes of transference can quite reasonably be discouraged lest their resolution add too much to the length of treatment. This type of therapy, with its physical and social supporting measures, is the bread-and-butter of the psychiatric clinic. It is particularly applicable to problems created by physical disease, and it is a kindly approach, for instance, to the elderly patient who is finding difficulty in accommodating himself to his failing powers. In psychotherapy the role of reason need not always, as a matter of principle, be subordinated to that of emotion, especially as a logical sequence enables patient and physician to keep the final aim in view. The fact that his work involves the manipulation of emotion and impulse does not absolve the therapist from planning his actual practice in a systematic way.

It is often thought that the application of psychotherapy to *high-grade mental defectives* is hardly worth while. Though the extent to which they can acquire an intellectual appreciation of their problems must be limited, this is not the same thing as absence of insight, and the latter is often, in terms of their own mode of thought, surprisingly good. The handicapped child who is brought up in an institution, and who in adolescence is turned out into a world whose written symbols he cannot interpret and whose customs are beyond his comprehension, is sometimes friendless and bewildered except when working in the task for which he has been trained. His chance of gaining the daily petty triumphs which sustain the average man is limited. The inability to keep his end up, to develop a sense of humour, or to understand abstract principles and conventional ideals, which are the penalties of his handicap, are complicated by the absence of a background of the normal affective relationships of childhood. Yet, if his language is understood, he is intensely rewarding as a patient because his demands are simple.

The Salvation Army have long known how to present the aims of life to the backward and to give them a sense of equality in the sight of God. They have thus had an enormous influence in preventing the backward from taking the foresightless path of delinquency. The psychotherapist must follow their example and learn to use the language of the backward if he is to restore to them a sense of security in their relations with their fellow men.

Psychoneurotic Symptoms with Organic Nervous Disease

One of the products of increasing knowledge of the effects of organic brain disease on the function of the psyche is the recognition not only that structural change often seems to predispose the individual to psychoneurotic reactions, but that it is often complicated by a functional overlay due to failure to adjust to the neurological handicap. In senile and arteriopathic dementia, and especially in the presenile deteriorations, pathological mental mechanisms of a very simple kind are frequently seen and if the dual nature of the process at work is understood, psychotherapy is remarkably effective, even though it may have to be superficial and didactic. The so-called degenerative hysterias found in association with chronic encephalitis, epilepsy, disseminated sclerosis, or other chronic processes, with their gross functional symptoms and childish behaviour, are remarkably easy to treat by direct suggestion and regime. The didactic approach appeals to the " concrete attitude " which so often develops in the course of organic brain disease.

In *psychosomatic disorders*, if exclusive stress is laid on purely psychological factors and the importance of organic predispositions and precipitating factors is ignored, mistakes will inevitably be made. The large-scale treatment of effort syndrome during the war did a great deal to convince physicians of the possibilities of the psychological approach and the increasing knowledge of the neuroendocrine links between mental stress and its somatic counterparts provide a rationale for further development in this field. But it is essential that anyone who undertakes treatment even of such conditions as da Costa's syndrome, functional indigestion, mucous colitis, eczema and enuresis, with their obvious psychogenic elements, should be fully aware of the physiology of the processes of which they are pathological caricatures. These often prove to be somatic " fractionations " of the anxiety syndrome and, as they are usually determined by conflicts of a kind not difficult to bring to the surface, treatment often has very satisfactory results. The same cannot be said of the treatment of hypertension, or of gastric ulcer, which, although obviously influenced in their course by psychological factors, are very uncertain in their response to psychotherapy. Those who advocate full psychoanalysis for these disorders seem to be motivated more by faith in the method than by any study of the results.

The psychotherapy of *delinquents* brings into relief a special problem that exists elsewhere in psychotherapy as well. As physicians we are concerned with the mental health of each patient as an individual, and as citizens we are concerned with the influence of his illness on others and on society. Where the aims of treatment in the two fields cannot be achieved in the same operation, we sometimes have conflicts of our own to solve as to what extent must we expect society to adapt to the patient and to what extent must we adapt the patient to society. No delinquent can be considered out of his environment so that the therapist who chooses to treat him must know something of the background and the language of the antisocial. Older but well-tried methods of approach—penal sanctions and religious influences, for instance—are not to be set aside at once because the present trend is psychodynamic. The therapist cannot afford to isolate or overprotect his patient, but must keep him in contact with society so that its influence and its sanctions can be felt at all levels of his mental life, conscious and unconscious.

The Patient who Asks for Psychotherapy

From time to time we have to consider how far the patient's own request for psychological treatment is an indication of his need for it. If cure is improbable, the amount of a physician's time which should be spent on consolation is a matter for the individual, provided that the application of comfort does not delay other necessary treatment. We must realise with Sophocles' Ajax that " it is not the part of a sound physician to wail incantations over a lesion that calls for the knife ", for the request for a gentler approach may be the patient's personal defence against the realisation that something more serious is amiss. The way in which an intelligent prepsychotic will sometimes welcome a diagnosis of

psychoneurosis and submit himself to treatment suggests the avoidance of a painful insight. Like the patient who has learnt that his malignant disease is inoperable and who has developed an intense belief in divine healing, it is not treatment that he seeks but magic, and psychiatry must often disappoint by offering the staff of Æsculapius to those who would prefer the wand of Merlin. Comforters, too, like indulgent parents, may render the comforted less sensible to their obligations to others. In some contemporary cultures the patient with means can buy psychotherapeutic cheer as he might buy alcohol, and the longer and gentler methods are sometimes used for no other purpose than to provide companionship with discussion of the patient's own favourite topic, himself. Those who demand and receive such treatment are customers rather than patients, and its provision is no part of medical psychotherapy which subscribes to the Hippocratic ideal.

Nevertheless there are many who, while not in serious danger of breakdown, have pressed on too fast in search of their immediate goals and who realise that they must now look back and come to terms with the forces which drive them and allow the following shadow of themselves to catch up with the substance. For, as Lucretius observed long ago:

> " So each man strives to flee that secret foe
> Which is himself. But move he swift or slow
> That self forever punctual at his heels
> Never for one short hour will let him go."

In general, the patient who is worried and who is prepared to make an effort, if only he can learn the kind of effort to make, is worth a more personal approach than the one who wishes to leave the whole matter to the psychotherapist. On the whole, the patient who asks for psychotherapy deserves to have his claims carefully examined, for his request may be both a symptom of disorder and a signal of distress.

The Individual Approach of the Psychotherapist

When he is actually engaged in psychotherapy, the physician's attitude of mind has to be very different from his critical objectivity at the diagnostic stage. If his role is to carry conviction with the patient, he must believe in what he is doing, and it is quite reasonable for him to choose some system or frame of reference to simplify his tactical thinking at the time. But the therapist who will use only his own method, in the face of symptoms requiring imposed psychotherapy or drug treatment, is comparable to a sportsman who will not shoot a sitting bird even though he and his party are starving. The treatment of illness is too difficult and serious a matter to be regarded as a sporting contest. Psychotherapy is real life, and those who employ it must use every means they can command against the common enemy. They may have to believe that no situation is hopeless. Marshal Foch's (Aston 1929)

> " Mon centre cède, ma droite recule, situation excellente. J'attaque!"

is in the very spirit of active psychotherapy. Although there seems to be little objection to the psychotherapist aligning his practice with that of a particular school, or on the other hand trying to make use of those features which he considers most useful in each, there can surely be no good reason for the confusion of systems and terminologies which is to be found. One sometimes encounters a sort of bewildered and polyglot eclecticism which expresses itself in mixed metaphors and descriptive terms, euphonious enough if said quickly, but at which the mind boggles if it seeks their abstract meaning. " Psycho-allergy " and " a hernia of the unconscious " are early examples. " Guilty feedback " and " abreaction at the diencephalic level " are more up-to-date specimens.

Psychotherapy is, apart from the few specific treatments in psychiatry, still the most potent force we possess for both cure and comfort. It is hard work, does harm less often than most forms of treatment, and is often strikingly successful. A psychotherapist must be prepared to identify himself very fully with the life and interests of his patient, must be nimble in penetrating his defences and evasions, and must be quick to learn his language. His work is to treat and not to judge, and it must not upset him to realise that his patient in many respects may be a better man than he. Most important of all, he must know when to stop and learn how to leave his patient content to be no more than Nature made him.

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PHENMETRAZINE HYDROCHLORIDE AND METHYLCELLULOSE IN THE TREATMENT OF "REFRACTORY" OBESITY

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To lose weight obese people must reduce their caloric intake to a level much below their current energy expenditure. Many, however, are either unable or unwilling to curb their appetites sufficiently, despite continued dietetic advice and encouragement. Too often their despairing medical attendant feels obliged to prescribe some drug for them—as an adjunct to dietetic advice—in the hope that it may reduce their appetite.

Thyroid preparations are valueless in the treatment of obesity (Edwards and Swyer 1950), except when there is coincident hypothyroidism. Amphetamine or dexamphetamine sulphates *B.P.* are still often prescribed to suppress excessive appetite, though they may not be entirely free from the dangers of habituation and toxicity (Aldersberg and Mayer 1949).

Two preparations more recently recommended as adjuncts to dietary treatment are phenmetrazine hydrochloride (' Preludin ') and methylcellulose (' Celevac '). The former is said to possess the appetite-reducing powers of the amphetamines without their undesirable attributes. Methylcellulose is an inert indigestible substance which swells up in the stomach and small

TABLE I—DATA CONCERNING THE THREE GROUPS OF PATIENTS

—	Group A	Group B	Group C
No. of patients:			
Totals	25	32	28
Females	22	28	24
Males	3	4	4
Diabetics:			
No.*	15 (*4*)	15 (*3*)	17 (*3*)
Age (yr.)	59·2 (*39–72*)	56·8 (*38–78*)	58·0 (*32–74*)
Body-weight (lb.):†			
1 yr. before trial	183·2±16·6 (*156–209*)	187·8±22·8 (*153–251*)	187·7±18·7 (*156–232*)
Change in yr. preceding trial	+1·1±8·6 (*−15–+19*)	−0·7±7·9 (*−12–+17*)	−1·8±6·0 (*−10–+9*)
At start of trial	184·3±16·0 (*162–218*)	187·1±19·7 (*156–242*)	185·9±17·4 (*162–224*)
"Standard weight" ‡	144·1±9·7 (*131–178*)	141·4±7·5 (*121–162*)	144·1±8·7 (*132–169*)
Wt at start of trial as % of standard	128·1±9·9 (*115–155*)	132·1±11·9 (*117–164*)	129·5±13·1 (*115–156*)
Excess wt at start of trial	40·2±13·6 (*22–74*)	45·7±16·6 (*23–80*)	41·8±18·1 (*20–75*)

* Numbers in parentheses are those taking insulin.
† Values are means, standard deviations, and ranges.
‡ Standard weight for each patient was derived from tables of the U.S.A. Medico-Actuarial Investigation, New York, 1912.

intestine and thus, if taken with water before meals, might produce a sense of repletion.

We report the results of a controlled double-blind trial of phenmetrazine and methylcellulose as adjuncts in the treatment of obese outpatients whose obesity had proved refractory to routine dietetic advice.

Methods

The records of the dietetic outpatient department were searched for patients treated for obesity over the previous year who had failed to lose weight in the past three months, despite the prescription of reducing diets providing 1100–1600 Calories a day. The first 92 patients who satisfied this criterion were taken. 5 were rejected because they were not sufficiently overweight. 2 more had to be withdrawn during the trial: 1 became pregnant, the other developed hypertensive heart-failure. All the remaining 85 were visibly obese; the obesity of 47 was, not unexpectedly, accompanied by mild diabetes, but only 10 were taking insulin, the small dose of which was not altered during the trial. They were divided into three deliberately matched groups (A, B, and C); none defaulted from the trial. The essential facts about these patients are set out in table I.

Initial Procedure

The patients were invited to attend special sessions of the clinic reserved for the study. Their previous clinical history and present physical status were recorded; blood glucose and cholesterol levels were determined. They were weighed in indoor clothing on a regularly standardised lever-type balance.

The actual diet being eaten by each was assessed from the dietary history, which was subsequently cross-checked independently by two or more dietitians; only a few frankly admitted to eating much more than the diet allowed. All were then reinstructed in the diet previously prescribed, exhorted to adhere to it, and told that they were to be given some tablets which might or might not assist them to do so.

Tablets Administered

These were of 4 kinds:

(1) Pink-coloured tablets each containing 0·5 g. of methylcellulose. Three of these were taken three times daily with a glassful of warm water half an hour before each of the three main meals.

(2) Dummy tablets made of lactose of the same size, shape, and colour as (1) and taken in the same way.

(3) Small white tablets each containing 25 mg. of phenmetrazine hydrochloride. During the second stage of the trial (period 2, table II) the patient was instructed to take one twice daily with a glassful of warm water half an hour before breakfast, the midday meal, or the evening meal, depending on which were the two largest meals. The second dose was never taken later than 6 P.M. Later in the trial (period 3, table II) one tablet was prescribed three times daily before each main meal.

(4) Dummy lactose tablets identical in appearance with (3), and taken in the same way.

Conduct of Trial

Each patient was weighed at fortnightly intervals and afterwards interviewed by one of us (L. J. P. D. or A. P. M.), the purpose being to stress the importance of losing weight and of keeping to the diet. At each attendance the patients were given only enough of the appropriate tablets to last until the date of their next visit, but again without any promise of their efficacy. The trial was divided into three periods as follows:

Period 1 (4 weeks).—All the patients received dummy tablets, simulating either methylcellulose or phenmetrazine, to assess the possible influence of special attention and new treatment in encouraging them to adhere more strictly to their diets.

Period 2 (8 weeks).—The patients in groups B and C were given active methylcellulose and phenmetrazine respectively, while those in group A continued to take one or other of the two kinds of dummies. This change was carried out by one of us (K. R.) without informing either the patient or her medical colleagues (L. J. P. D. and A. P. M.), who were unaware of the group to which each patient had been assigned or of whether any one patient was receiving active or dummy tablets. In this way a "double-blind" trial was assured, and the response to treatment could be assessed without prejudice born of pre-knowledge of the medication given.

Period 3 (8 weeks).—A few days before the end of period 2 a preliminary analysis of the data was made by one of us (L. J. P. D.) without disclosure of the identity of the patients. This showed that methylcellulose was having little effect—in contrast to the phenmetrazine—on the weight of the patients. The original plan to give patients in group A active phenmetrazine or methylcellulose and those in groups B and C dummy methylcellulose and phenmetrazine respectively was altered; patients in groups A and B were instead given active phenmetrazine. However, all patients in group B and half of group A had been taking active or dummy methylcellulose and would therefore appreciate that they were being given different tablets. Therefore half of those in group C were given dummy phenmetrazine and the remainder dummy methylcellulose tablets so that any effect of a recognised substitution would be revealed. These substitutions were again made by K. R.

TABLE II—INFLUENCE OF ADMINISTRATION OF THE SEVERAL PREPARATIONS ON THE BODY-WEIGHT (LB.) OF THE THREE GROUPS OF PATIENTS (VALUES ARE MEANS, STANDARD DEVIATIONS, AND RANGE)

Period	—	Group A	Group B	Group C
	Initial weight	184·3±16·0 (*162–218*)	187·1±19·7 (*156–242*)	185·9±17·4 (*162–224*)
1	After 4 weeks' administration of:	Dummy phenmetrazine or dummy methylcellulose	Dummy methylcellulose	Dummy phenmetrazine
	Weight	182·8±17·0 (*159–219*)	186·1±20·6 (*158–243*)	185·9±18·0 (*159–225*)
	Change in weight	−1·5±2·9 (−11–+3)	−1·0±2·9 (*−7–+5*)	0±2·1 (*−5–+4*)
2	After 8 weeks' administration of:	Dummy phenmetrazine or dummy methylcellulose	Active methylcellulose	Active phenmetrazine
	Weight	182·6±18·0 (*155–219*)	185·5±20·3 (*158–244*)	179·9±18·4 (*151–217*)
	Change in weight	−0·2±2·7 (*−8–+3*)	−0·6±4·1 (*−13–+7*)	−6·0±3·2 (*−13–−1*)
3	After 8 weeks' administration of:	Active phenmetrazine	Active phenmetrazine	Dummy phenmetrazine or dummy methylcellulose
	Weight	178·5±17·6 (*152–216*)	182·7±21·5 (*155–255*)	181·9±17·4 (*152–220*)
	Change in weight	−4·1±4·6 (*−20–+7*)	−2·8±5·3 (*−13–+11*)	+2·0±3·2 (*−6–+8*)

Results

Changes in Weight

Table II sets out the changes in weight. In period 1, when all the patients were receiving dummy tablets, only a few lost weight. In period 2 there was little weight change in most of those receiving methylcellulose (group B) and those continuing to receive dummy tablets (group A), whereas there was a mean loss of 6·0 lb. in the patients receiving phenmetrazine hydrochloride (group C). This loss was statistically highly significant ($P < 0.01$) by comparison with that of the other two groups in the same period.

In period 3, those who had lost weight while receiving phenmetrazine (group C) showed a mean gain of 2·0 lb. when returned to dummy tablets. Those who had failed to show a significant mean loss of weight in the previous eight weeks when taking dummy tablets (group A) or methylcellulose (group B) now showed a mean loss of 4·1 lb. and 2·8 lb. respectively, when transferred to phenmetrazine. The mean weight gain of those in group C was statistically highly significant by comparison both with their mean weight loss in the previous eight weeks and with the mean weight losses of groups A and B in period 3 ($P < 0.01$). The weight losses of those in groups A and B also differed significantly from their losses in the previous eight weeks ($P < 0.01$).

During period 3 the mean weight loss (−3·6 lb.) of those in group A who had previously been taking the dummy methylcellulose, and had thus been aware of the change in tablets, did not differ significantly from that (−4·5 lb.) of those previously taking dummy phenmetrazine and who did not notice any change in medication. Similarly there was little difference in the weight changes between those in group C who were given methylcellulose (−1·7 lb.) and those given phenmetrazine dummy tablets (−2·3 lb.).

The mean weight loss of groups A and B when given phenmetrazine in period 3 was less than that of group C given the same compound in period 2, although the latter were taking a smaller dose (25 mg. twice daily as opposed to 25 mg. three times daily). There are several possible explanations of this. The trial began towards the end of May, 1957; period 3 was thus in the autumn and many patients had begun to wear heavier clothing. They were also likely to be consuming more calories, perhaps because the weather was colder, but more probably because non-fattening vegetables and other seasonal low-calorie foods were now more expensive and difficult to obtain. Moreover their interest in the study and their very limited initial enthusiasm for dietary discipline had noticeably deteriorated.

Other Changes

Blood-pressure was checked regularly; no important alterations were observed. Of the 28 patients in group C, however, 8 showed an apparent fall both in systolic and diastolic pressure after receiving phenmetrazine for eight weeks (end of period 2), by comparison with the initial blood-pressure at the start of the trial. None in this group showed any rise in blood-pressure.

The *blood glucose and cholesterol* levels changed considerably in some patients during the trial. However, there was no consistent trend, either up or down, nor any apparent relation to losses or gains in weight.

Symptoms and Side-effects

Any subjective effect attributed by the patients to the tablets was noted; but, apart from asking whether they felt less hungry or more able to adhere to the diet, direct inquiry for side-effects previously reported in published accounts was especially avoided.

48 patients noticed no effects from taking any one of the four different preparations given. Only 5 said that they felt less hungry; they were taking phenmetrazine at the time. 2 patients felt more hungry on methycellulose, and another complained of nausea. Generally the change from dummy to active tablets and vice versa went unremarked by the patients, though some who chewed rather than swallowed their tablets noticed the bitter taste of phenmetrazine and the difference in consistence between dummy and active methylcellulose.

Of the 57 patients receiving phenmetrazine thrice daily (period 3) 5 complained of insomnia, while 7 others complained of some headache, lightheadedness, dizziness, nervousness, or excitability; 9 patients receiving dummy tablets had similar complaints but not insomnia. Consequently with the exception of insomnia following an evening dose of phenmetrazine, little significance can be attached to these symptoms.

Several patients assured us that they felt better as a result of taking the tablets, though sometimes it subsequently transpired that they were taking dummy tablets at the time. No distinct stimulation or euphoria was noted in those taking phenmetrazine.

2 patients, after taking phenmetrazine for six weeks, complained of palpitation and a return of previous angina pectoris. These complaints ceased when this medication was subsequently stopped.

Discussion

Under the conditions of this trial phenmetrazine effected a statistically significant mean loss of weight in obese patients whereas a preparation of methylcellulose had no such effect.

Both preparations were given a very severe test. An attempt to treat the patients by conventional dietetic advice over the previous year had been unsuccessful, and none had lost weight in the past three months. Moreover, their mean weight loss in the first month of the study when dummy tablets were given was negligible. Although weight loss by dietary restriction may be delayed for several weeks, those in groups A and B showed no substantial loss in the first three months of treatment. The patients were therefore not much influenced by the increased attention or the giving of tablets; their obesity may well be described as refractory.

Dexamphetamine, in similar short-term studies, promoted a weight loss of about the same amount (Edwards and Swyer 1950) and its undesirable attributes may be unduly emphasised. We know of no evidence that amphetamine or dexamphetamine sulphates are less effective than phenmetrazine, which is three to six times more expensive. In Scotland the cost to the National Health Service of dispensing, on prescription, 100 tablets of these preparations is as follows:

Preludin tablets, 25 mg.	18*s.* 3*d.*
Tab. amphetamine sulphate *B.N.F.* 5 mg.	3*s.* 5½*d.*
Tab. dexamphetamine sulphate *B.N.F.* or *B.P.C. addendum* (1954) 5 mg.	2*s.* 9½*d.*
Dexedrine tablets, 5 mg.	5*s.* 8*d.*

It is remarkable that so few (5 of 85) patients admitted that they had less desire for food when taking phenmetrazine; the compound is considered either to inhibit appetite or to produce early satiety. However, Edwards

and Swyer (1950) found that dexamphetamine seldom diminished subjective feelings of hunger in obese patients who lost weight when taking it.

In this trial phenmetrazine produced no important side-effects except insomnia when taken in a dose of 25 mg. thrice daily. This is in keeping with previous reports (Martel 1957, Barnes 1958). However, 7 patients have since asked for a renewed supply of the drug, which raises the serious question of addiction. Kahan and Mullins (1958), Evans (1959), and Glatt (1959) have all described patients, not previously psychotic, who began taking phenmetrazine tablets for slimming but afterwards used them as " pep pills ", gradually increasing the dose up to 20 tablets (0·5 g.) or more a day. They developed a psychotic schizophrenic type of illness, often associated with delusions and hallucinations, lasting weeks or months, resembling the psychosis caused by addiction to amphetamine. Incidentally the cost of the pills can lead to poverty and consequent ruin.

It must be stressed that the phenmetrazine was given for periods of only two months and that the weight loss, though statistically significant, was disappointingly small. There is still no acceptable evidence of the efficacy of phenmetrazine given for longer periods. Prolonged studies have, however, shown that in the long run obese patients treated with amphetamine or dexamphetamine and diet lost no more weight than those treated with diet alone (Aldersberg and Mayer 1949). There is no reason to expect long-term treatment with phenmetrazine to be any better.

It has been suggested that about a quarter of patients given phenmetrazine for two months or so become accustomed to food restriction and thus have no further need to take the drug (Martel 1957). The mean gain in weight of patients in group C during period 3 does not support this view.

Summary

A double-blind clinical trial of methylcellulose and phenmetrazine hydrochloride was carried out on 85 obese outpatients who had proved refractory to dietary advice alone.

Methylcellulose was ineffective. Phenmetrazine hydrochloride produced a very small, but statistically significant, mean loss of weight in two months.

No important side-effects resulted from the use of phenmetrazine hydrochloride in a dose of 25 mg. twice daily. 5 patients complained of insomnia and 2 of a return of angina pectoris when the dose was 25 mg. thrice daily.

Because of its cost, its small influence on appetite, and the dangers of addiction, we do not regard phenmetrazine as a good drug for the routine treatment of obese patients.

We thank Sir Derek Dunlop for his encouragement and advice; and Miss E. M. Wilson and Miss E. N. Owles for much help with the dietetic interviews. Harker Stagg Bros. supplied the methylcellulose in the form of ' Celevac ' tablets with dummy tablets to match. The phenmetrazine hydrochloride (' Preludin ') and matching dummy tablets were provided by Pfizer Ltd. and Boehringer Sohn.

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PHENMETRAZINE AND DEXAMPHETAMINE IN THE MANAGEMENT OF OBESITY

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WHILE nobody seriously doubts that obese patients will lose weight when their intake of food is sufficiently curtailed, there is much difference of opinion as to the most satisfactory way of restricting the amount of food that they eat. Apart from the large variety of special diets in use, a number of drugs have been proposed as aids to weight reduction, in the belief that, if appetite could be depressed by this means, weight might be lost more consistently and more rapidly than is usual with conventional methods.

Amphetamine and *d*-amphetamine have been used for the suppression of appetite for many years; phenmetrazine (' Preludin '), an analogue with reduced sympathomimetic properties, was introduced in 1954 by Thomae and Wick for the same purpose. So far as we are aware, no direct comparison has been made of the value of phenmetrazine and *d*-amphetamine in the management of obesity. We now report the results of such a clinical trial, which also includes a comparison of the effects of these two drugs with those of inert tablets.

Methods

A " double-blind " procedure was used, so that the identity of the drug in use was unknown to the patient and to the doctor, and remained so until the conclusion of the trial. Three series of tablets of similar appearance were made up as follows: phenmetrazine hydrochloride 25 mg., dexamphetamine sulphate *B.P.C.* 5 mg., and a control tablet consisting of lactose, talc, starch, quassia, and magnesium stearate. A " cross-over " technique was employed in the administration of the tablets (Gaddum 1953), so that each patient received all three forms of treatment; in this way it was hoped to reduce errors due to differences in the response to each drug by individual patients.

Any patient referred to the dietetic department on account of obesity was accepted for study, provided they were considered to be sufficiently obese to justify the imposition of a dietary regimen providing 800–1000 calories for a period of eighteen weeks, and that their circumstances would allow them to attend the department regularly once a week for weighing. All were treated as outpatients, and they were advised to remain on the same diet throughout the investigation. A conventional reducing diet was prescribed which provided between 800 and 1020 calories daily according to the initial weight of the patient, consisting of carbohydrate 75–90 g., protein 45–52 g., and fat 38–50 g. approximately. Patients were instructed to take one of the tablets with which they were supplied half an hour before breakfast and half an hour before their midday meal.

All patients were treated for three consecutive periods of six weeks with one of each of the three types of tablet throughout each period. The order of administration of the tablets was determined before the beginning of the trial by preparing a table based on random numbers (Bradford Hill 1955), so that the sequence of administration of each drug was varied in a random manner.

Results

51 patients were accepted for the trial, and of these 37 completed the full period of study lasting eighteen weeks. Of these 37, 8 were males (average age 59·6 years, range 45–70) and 29 were females (average age 50·1 years, range 21–69).

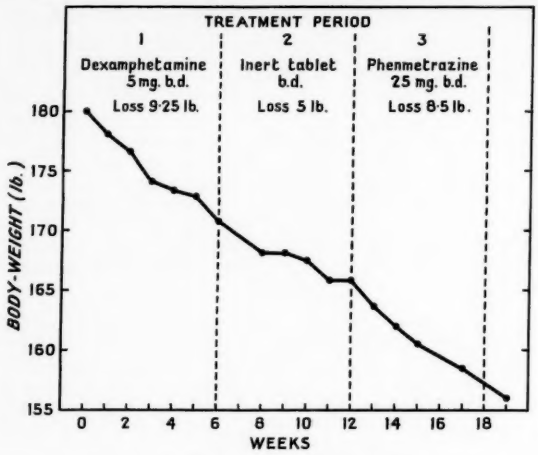

Fig. 1—Typical example of results.

The patient was a 56-year-old woman, height 5 ft. 8 in., ideal weight 140 lb. on a diet yielding 1018 calories a day.

A typical example is illustrated in fig. 1.

The patient was approximately 40 lb. overweight when first seen. She was treated with dexamphetamine, inert tablets, and phenmetrazine in that order, each for a period of six weeks. During the first period she lost 9·25 lb. (4·20 kg.) in weight, in the second period 5·0 lb. (2·26 kg.), and in the final period 8·5 lb. (3·85 kg.).

The results obtained in the three treatment groups, irrespective of the order in which the drugs were given, are shown in table I. The mean weight loss during six weeks' treatment with inert tablets was 4·76 lb. (2·16 kg.), with phenmetrazine 8·26 lb. (3·74 kg.), and with dexamphetamine 6·7 lb. (3·04 kg.).

TABLE I—LOSS OF WEIGHT DURING TREATMENT FOR PERIODS OF SIX WEEKS

—	Treatment		
	Inert tablets	Phenmetrazine 25 mg. b.d.	Dexamphetamine 5 mg. b.d.
No. of patients	37	37	37
Mean loss of weight per patient in 6 weeks (lb.):			
Amount	4·76	8·26	6·71
Standard error	±0·71	±0·70	±0·67
Range (lb.)	14·5—4·0	18·0—1·0	19·5—3·5

Analysis shows that the difference between the mean loss of weight during treatment with phenmetrazine and with inert tablets is highly significant; the difference between the mean loss of weight on inert tablets and on dexamphetamine is less, though still significant. Although the mean loss of weight during treatment with phenmetrazine is greater than with dexamphetamine, analysis shows that the difference between the means is not statistically significant.

In table II the results have been arranged to demonstrate the striking effect of time on the loss of weight,

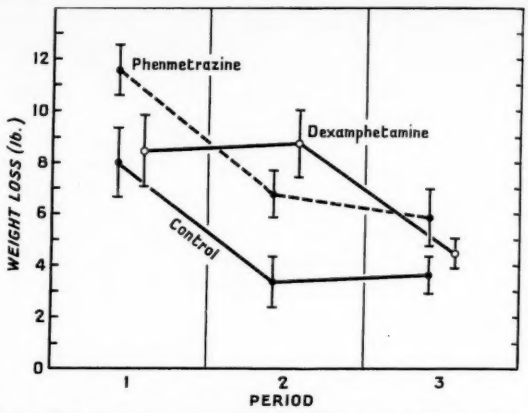

Fig. 2—Relation between drugs used and loss of weight in three successive periods of six weeks each (plotting-points show mean and vertical lines standard error).

irrespective of the identity of the drug in use. It is apparent that the loss of weight during the first period of six weeks is much greater than in either of the two succeeding periods.

The number of patients receiving each drug in each period, together with the mean loss of weight per patient during each period of treatment, is shown in table III.

TABLE II—LOSS OF WEIGHT DURING THREE SUCCESSIVE PERIODS, EACH OF SIX WEEKS, IRRESPECTIVE OF DRUG USED

—	Period		
	1	2	3
Mean loss of weight per patient per period (lb.):			
Amount	9·43	5·59	4·72
Standard error	±0·74	±0·70	±0·48
Range	19·5–1·5	14·5—4·0	12·5—3·0

Analysis of significance of difference between means:
Period 1 *v.* period 2 $t=5{\cdot}12$ ($P<0{\cdot}001$)
Period 2 *v.* period 3 $t=1{\cdot}09$ ($0{\cdot}3>P>0{\cdot}2$)

Since the precise effect of a treatment depended upon two things—namely, the kind of tablet taken and whether it was administered in the first, second, or third period—a more accurate judgment can be made if these two influences are disentangled. The regression of weight loss upon period of treatment proved not to be significantly different for the three kinds of tablet, so a common set of correction terms could be used. These were:

First six weeks	−2·85 lb.
Second six weeks	+0·99 lb.
Third six weeks	+1·86 lb.

When these correction terms are applied to the weight losses of the individual patients, the influence of period of treatment is counteracted, at any rate to a first approximation. Table IV gives the mean differences in the weight lost with and without the correction for the period of treatment. Although in two cases the correction slightly decreases the difference observed, the statistical significance of each difference has been appreciably

TABLE III—NUMBER OF PATIENTS AND MEAN WEIGHT LOSS IN EACH TREATMENT GROUP

—	Period 1			Period 2			Period 3		
	Inert tablets	Phenmetrazine	Dexamphetamine	Inert tablets	Phenmetrazine	Dexamphetamine	Inert tablets	Phenmetrazine	Dexamphetamine
No. of patients	11	14	12	17	12	8	9	11	17
Mean loss of weight (lb.) per patient per period of 6 weeks ..	7·9	11·5	8·4	3·3	6·7	8·7	3·6	5·9	4·5

TABLE IV—MEAN DIFFERENCES BETWEEN THE AMOUNT OF WEIGHT LOST DURING SIX WEEKS' TREATMENT WITH THREE DRUGS, BEFORE AND AFTER CORRECTION FOR THE ORDER IN WHICH THE DRUGS WERE GIVEN TO INDIVIDUAL PATIENTS (SEE TEXT)

—	Mean difference (lb.)		
	Inert tablets *v.* phenmetrazine	Inert tablets *v.* dexamphetamine	Dexamphetamine *v.* phenmetrazine
Uncorrected ..	3·507	1·926	1·378
Corrected ..	3·262	2·008	1·192

Analysis of Significance of the Differences between the Means:

	Uncorrected	*Corrected*
Inert tablets *v.* phenmetrazine	$t=3{\cdot}84$ ($P<0{\cdot}001$)	5·28($P<0{\cdot}001$)
Inert tablets *v.* dexamphetamine	$t=2{\cdot}05$ ($0{\cdot}05>P>0{\cdot}02$)	2·53($0{\cdot}02>P>0{\cdot}01$)
Dexamphetamine *v.* phenmetrazine	$t=1{\cdot}57$ ($0{\cdot}2>P>0{\cdot}1$)	1·76($0{\cdot}1>P>0{\cdot}05$)

TABLE V—WEIGHT LOST BY 14 DEFAULTERS WHILE THEY REMAINED UNDER OBSERVATION

—	Inert tablets	Phenmetrazine 25 mg. b.d.	Dexamphetamine 5 mg. b.d.
Mean weight loss (lb.) per patient per period of 6 weeks	4·2	9·0	6·0

increased by the removal of the effect of the order in which the treatments were given.

The results obtained in patients who failed to complete the eighteen weeks of study have not been taken into account in preparing tables I–IV. These results have been summarised in table V.

In fig. 2 we have summarised the results obtained with the three types of tablet in each period. As treatment continues, the amount of weight lost with each type of tablet is steadily reduced, and after twelve weeks the difference between the three becomes very small.

Discussion

This trial was designed to show whether two of the drugs commonly recommended in the management of obesity had any advantage over dietary restriction alone in ensuring or increasing loss of weight, and also to compare the relative efficacy of these two drugs. Under the conditions described the use of both dexamphetamine and phenmetrazine as well as inert tablets was associated with consistent loss of weight in the majority of patients. It would have been interesting to have included a fourth period on the same diet during which no treatment with any form of drug was given, but this would have interfered with the " double-blind " nature of the trial, and for this reason it was omitted. Both dexamphetamine and phenmetrazine were shown to be more effective than inert tablets, and in the doses used phenmetrazine was slightly more effective than dexamphetamine.

14 of the patients originally accepted for the trial defaulted at various stages of the eighteen weeks of study (table V), but in no case was the trial discontinued because of side-effects or at the suggestion of the observers. Up to the time that they defaulted, these patients were losing weight at a similar rate on each form of treatment to that of the patients who completed the trial. For this reason the defaulters are unlikely to have affected the validity of the conclusions based on the results obtained from those who completed eighteen weeks of study.

The remarkable reduction in the amount of weight lost by most of these patients in successive periods may not be due simply to weakening of resolve and failure to persist with the regimen. A considerable loss of body-water (" initial dehydration ") is known to occur when obese patients start treatment with reducing diets. This may be due to changing from a diet which includes a high intake of carbohydrate to a regimen on which the patient depends on endogenous fat for much of his energy requirements (Passmore, Strong, and Ritchie 1958). Such a mechanism could account for the striking difference in the mean loss of weight between the first and subsequent periods noted in table II.

It is evident from fig. 2 that after a period of twelve weeks the value of dexamphetamine and phenmetrazine in promoting loss of weight appears to be very limited, though in the period six to twelve weeks both compared favourably with the inert tablet.

We may conclude that many obese patients will lose weight satisfactorily if suitably advised and provided they are seen regularly at short intervals. Drugs of the type widely prescribed for the suppression of appetite have a limited place in the management of obesity, but they tend to be less effective when used for long periods.

The problems raised by comparison of the cost of these drugs and the dangers of addiction cannot be ignored. These have been discussed elsewhere by Duncan, Rose, and Meiklejohn (1960).

Summary

The value of dexamphetamine 5 mg. b.d. and phenmetrazine 25 mg. b.d. in promoting weight loss in obese patients has been compared with that of an inert tablet.

Phenmetrazine appeared to be slightly more effective than dexamphetamine, but both were more effective than the inert tablet.

Whatever the treatment used, loss of weight was greater during the first period of six weeks than in either of the two succeeding periods.

Acknowledgments are due to colleagues who permitted us to study patients under their care. We are particularly grateful to Miss A. H. Halley and her colleagues in the dietetic department for much help. Dr. F. R. Fletcher, of Messrs. Pfizer Ltd., kindly arranged the preparation of the tablets used in the trial. We are also indebted to Dr. B. Woolf, F.R.S.E., of the Department of Animal Genetics, for his advice on the preparation of table IV.

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THE DIURETIC ACTIVITY OF BENDROFLUAZIDE

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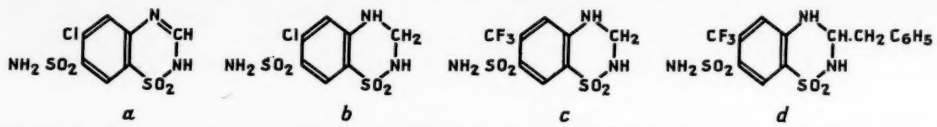
SINCE chlorothiazide was introduced by Novello and Sprague in 1957, the search for even more efficient oral diuretics of the benzothiadiazine group has advanced rapidly. Hydrochlorothiazide (Fleming et al. 1959) was soon followed by hydroflumethiazide (Blagg 1959, Edmonds and Wilson 1959, Kennedy et al. 1959), and these preparations, which have a similar action to chlorothiazide, were shown to be about ten times more potent on a weight-for-weight basis.



a *b* *c* *d*

Fig. 1—Chemical structure of (*a*) chlorothiazide, (*b*) hydrochlorothiazide, (*c*) hydroflumethiazide, and (*d*) bendrofluazide.

Bendrofluazide ('Aprinox') is a further benzothiadiazine derivative which has still greater potency, weight for weight, than either hydrochlorothiazide or hydroflumethiazide. The structural relations of chlorothiazide, hydrochlorothiazide, hydroflumethiazide, and bendrofluazide is shown in fig. 1.

We report here the results of volumetric and biochemical studies on nineteen œdematous patients and on two healthy male subjects, who received in all 59 doses of bendrofluazide. Fourteen patients had congestive cardiac failure, three had hepatic cirrhosis, one had the nephrotic syndrome, and one woman had premenstrual œdema.

Methods

The doses of bendrofluazide were 5 mg. (5 times), 7·5 mg. (50 times), or 10 mg. (4 times).

Detailed biochemical and volumetric analyses were performed on the fourteen œdematous patients after a single dose of bendrofluazide (table I). Urine was collected for a control period of 24 hours before the drug was given (period I), and for two consecutive 12-hour periods thereafter (periods II and III), except in one patient (case 14) in whom a single 24-hour collection was made. Blood samples were taken just before bendrofluazide was given, and again 24 hours later. The urine collections were analysed in respect of volume, sodium, chloride, potassium, and inorganic-phosphorus content. The urea, sodium, chloride, and potassium contents of the blood samples were determined.

In a group of seven œdematous patients the serum-potassium level was determined before and after several doses of bendrofluazide (table II). Two of them were also submitted to detailed biochemical studies after a single dose.

Two healthy young men were each given 5 mg., 7·5 mg., and 10 mg. of bendrofluazide, with at least 7 days between each dose (table III). The urine was collected as before during periods I, II, and III, and the content of sodium, chloride,

TABLE I—BIOCHEMISTRY AND URINARY VOLUME STUDIES IN FOURTEEN PATIENTS BEFORE AND AFTER BENDROFLUAZIDE

Case no.	Sex	Age (yrs.)	Diagnosis	Dose (mg.)	Period of study	Urine					Blood (plasma)
						(ml.)	Volume (ml. per hr.)	Potassium (mEq. per hr.)	Sodium (mEq. per hr.)	Chloride (mEq. per hr.)	Potassium (mEq. per litre)
1	M	35	Congestive cardiac failure Rheumatic heart-disease	5·0	I	2270	94·6	2·98	9·72	8·85	4·4
					II	1505	125·3	3·51	12·91	13·87	
					III	1080	90·0	1·75	7·47	6·27	4·2
2	F	70	Congestive cardiac failure Ischæmic heart-disease	5·0	I	1390	57·9	1·59	5·42	4·73	4·8
					II	980	81·7	1·88	9·33	9·07	
					III	950	79·3	1·67	7·95	6·95	4·7
3	F	45	Premenstrual œdema	5·0	I	1615	67·3	1·11	6·77	5·73	4·5
					II	2133	177·5	1·91	23·00	21·30	
					III	1250	104·2	1·41	12·14	9·63	4·1
4	M	35	Congestive cardiac failure Rheumatic heart-disease	7·5	I	1480	61·6	1·91	6·47	4·24	4·3
					II	1745	145·3	4·07	23·40	21·68	
					III	450	37·5	0·96	4·36	4·40	4·2
5	M	59	Cirrhosis of liver	7·5	I	410	17·1	0·27	1·95	1·71	4·5
					II	1000	83·3	1·94	16·50	17·80	
					III	650	54·2	1·30	5·25	6·44	4·2
6	F	67	Congestive cardiac failure Pernicious anæmia	7·5	I	1950	81·2	1·28	7·56	8·12	3·8
					II	2650	220·8	1·86	22·40	25·10	
					III	1965	163·7	1·27	17·58	16·23	3·8
7	F	64	Congestive cardiac failure Rheumatic heart-disease	7·5	I	2110	87·9	1·72	6·16	6·12	4·5
					II	1230	102·5	1·43	11·83	10·05	
					III	1590	132·5	1·92	12·07	13·21	4·0
8	F	61	Congestive cardiac failure Ischæmic heart-desease	7·5	I	1470	61·3	1·23	3·51	3·60	4·4
					II	1810	151·0	2·42	16·18	17·15	
					III	975	81·3	1·87	10·70	11·33	4·0
9	F	62	Cirrhosis of liver	7·5	I	770	29·6	1·19	3·21	2·34	4·6
					II	790	65·8	2·14	10·59	10·57	
					III	760	63·3	2·44	6·06	6·41	4·2
10	F	43	Congestive cardiac failure Rheumatic heart-disease	7·5	I	1315	54·7	2·52	2·68	3·02	5·2
					II	1120	93·2	3·92	10·64	12·80	
					III	680	56·6	1·62	2·91	3·63	4·6
11	F	72	Congestive cardiac failure Thyrotoxicosis	7·5	I	595	24·8	0·63	1·38	0·56	3·6
					II	457	38·0	1·29	6·40	5·68	
					III	1200	100·0	1·15	8·40	6·49	3·8
12	F	47	Cirrhosis of liver	7·5	I	2090	87·3	1·53	13·4	12·57	4·3
					II	2310	192·5	2·98	36·83	28·93	
					III	910	75·8	1·32	10·61	8·40	4·3
Mean values of above studies for 5 mg. dose					I	—	73·27	1·89	7·30	6·43	4·57
					II		128·17	2·63	15·08	14·75	
					III		90·50	1·61	9·19	8·45	4·33
„ „ „ „ „ „ 7·5 mg. „					I		56·06	1·36	5·14	4·69	4·35
					II	—	121·32	2·45	17·19	16·64	
					III		84·98	1·54	8·66	8·50	4·12
Range (5 mg. dose)					I		57·9–94·6	1·11–2·98	5·42–9·72	4·73–8·85	4·4–4·8
					II	—	81·7–177·5	1·88–3·51	9·33–23·00	9·07–21·30	
					III		79·3–104·2	1·41–1·76	7·47–12·14	6·27–9·63	4·1–4·7
„ (7·5 mg. dose)					I		17·1–87·9	0·27–2·52	1·95–13·4	0·55–12·57	3·6–5·2
					II	—	38·0–220·8	1·43–4·07	6·4–36·83	5·68–28·93	
					III		37·5–163·7	0·96–2·44	2·91–17·58	3·63–16·23	3·8–4·6
13	M	55	Nephrotic syndrome	10	I	850	35·4	1·03	1·06	1·50	2·5*
					II	1200	100·0	2·38	7·35	7·40	
					III	1600	135·0	2·56	9·45	9·92	3·0
14	M	49	Congestive cardiac failure Rheumatic heart-disease Thyrotoxicosis	10	I	910	37·9	1·39	1·43	1·26	4·4
					II, III	1400	58·4	1·79	6·30	7·35	4·3

* Potassium chloride 6 g. given by mouth in the following 24 hours.

TABLE II—PLASMA-POTASSIUM LEVELS BEFORE AND AFTER SEVERAL DOSES OF BENDROFLUAZIDE IN SEVEN PATIENTS WITH CONGESTIVE CARDIAC FAILURE

Case no.	Sex	Age (years)	Diagnosis	Dosage of bendrofluazide	Plasma-potassium (mEq. per litre)		Comments
					Before	After	
6	F	67	Congestive cardiac failure Pernicious anæmia	5 doses of 7·5 mg. in 11 days	3·75	4·6	Œdema disappeared; good hæmatological response to vitamin B_{12}
7	F	64	Congestive cardiac failure Rheumatic heart-disease	8 doses of 7·5 mg. in 25 days	4·0	4·6	Œdema disappeared; digoxin also given
15	F	76	Congestive cardiac failure Pernicious anæmia	6 doses of 7·5 mg. in 15 days	3·4	4·2	5 g. potassium chloride given on 1st day of bendrofluazide therapy; digoxin also given; became free from œdema
16	F	34	Congestive cardiac failure Rheumatic heart-disease	7 doses of 7·5 mg. in 18 days	4·6	4·7	Also given digoxin; became free from œdema
17	F	67	Congestive cardiac failure Myocardial infarction	5 doses of 7·5 mg. in 9 days	4·7	4·6	Œdema disappeared; having anticoagulants but not digoxin
18	F	65	Congestive cardiac failure Ischæmic heart-disease	3 doses of 7·5 mg. in 8 days	4·6	4·7	Digoxin also given; became free from œdema
19	F	42	Congestive cardiac failure Rheumatic heart-disease	5 doses of 7·5 mg. in 12 days	5·5	4·8	Œdema disappeared; digoxin also given

potassium, inorganic phosphorus, and the volume, were estimated. A dose-response curve was plotted.

Flame photometry was used for the sodium and potassium estimations, silver-nitrate titration for chloride estimations (Wilson and Ball 1928), the method of Archer and Robb (1925) for urea estimations, and the method of Fiske and Subbarow (1925) for measuring inorganic phosphorus.

Results

The detailed volumetric and biochemical findings are given in the tables.

Diuresis and Dose of Bendrofluazide

With the 5 mg. dose of bendrofluazide a definite diuresis was obtained in all three œdematous patients (table I, cases 1–3) studied intensively (the mean volume in ml. per hour was: period I, 73·27; II, 128·17; III, 90·50). One of the two normal subjects had a diuresis (table III).

A diuresis was obtained in all œdematous patients (table I, cases 4-12) who had the 7·5 mg. dose, and in the majority it was considerable (the mean volume in ml. per hour was period I, 56·06; II, 121·32; III, 84·98). A good diuresis was also obtained in the two normal subjects with a 7·5 mg. dose (the mean volume in ml. per hour was period I, 40·2; II, 136·3; III, 58·3).

TABLE III—URINARY VOLUME AND BIOCHEMISTRY IN TWO NORMAL SUBJECTS AFTER DIFFERING DOSES OF 5 MG., 7·5 MG., AND 10 MG. BENDROFLUAZIDE

Subject	Dose (mg.)	Period of study	Urine				
			Volume (ml.)	Volume (ml. per hr.)	Potassium (mEq. per hr.)	Sodium (mEq. per hr.)	Chloride (mEq. per hr.)
Normal male; aged 25; body-weight 75·0 kg.	5	I	1675	69·8	4·64	9·78	10·57
		II	1035	86·1	4·96	17·07	23·4
		III	390	32·5	1·87	5·36	6·27
	7·5	I	990	41·2	3·55	7·84	7·22
		II	1680	140·0	4·75	31·68	31·90
		III	970	80·8	1·80	9·82	9·94
	10	I	1070	45·0	3·64	8·60	9·98
		II	1550	129·0	4·84	35·50	36·62
		III	1280	104·0	2·91	14·92	15·36
Normal male; aged 23; body-weight 74·1 kg.	5	I	1240	51·7	1·76	5·05	5·44
		II	1140	95·0	4·85	14·29	18·45
		III	900	75·0	1·60	8·47	6·76
	7·5	I	930	39·2	2·35	6·75	6·70
		II	1590	132·5	2·82	23·32	22·78
		III	430	35·8	1·43	6·18	6·22
	10	I	1160	48·4	1·86	5·75	5·74
		II	1720	143·2	2·65	21·70	24·15
		III	410	34·2	1·35	4·63	4·56
Mean values of above studies	5	I	..	60·75	3·20	7·42	8·00
		II	..	90·55	4·90	15·68	20·93
		III	..	53·75	1·73	6·92	6·52
	7·5	I	..	40·2	2·95	7·30	6·96
		II	..	136·3	3·78	27·50	27·34
		III	..	58·3	1·62	8·00	8·08
	10	I	..	46·7	2·75	7·18	7·86
		II	..	136·1	3·25	28·60	30·38
		III	..	70·4	2·13	9·78	9·96

In the two normal subjects the diuresis after the 10 mg. dose of bendrofluazide was not appreciably greater than with the 7·5 mg. dose (fig. 2). Likewise, the diuresis resulting from 10 mg. in two œdematous patients (table I, cases 13 and 14) was of the same order as that in the majority of œdematous patients who had 7·5 mg.

Time of diuresis.—In most of the patients studied the maximum diuresis was in the first 12 hours (period II) after bendrofluazide was given, while the diuresis was less, although still appreciable, in the second 12 hours (period III). In two patients (cases 7 and 11) with congestive cardiac failure, and in one (case 13) with the nephrotic syndrome, the diuresis was greater in the second 12 hours (period III).

Sodium and Chloride Excretion

Urinary sodium and chloride were both greatly increased after bendrofluazide. With the 5 mg. dose the mean increase in both sodium and chloride was about twofold (7·30–15·08 mEq. per hour of sodium, and 6·43–14·75 mEq. per hour of chloride). With the 7·5 mg. dose the mean sodium increase was more than threefold (5·14–17·19 mEq. per hour), and the mean chloride increase was fourfold (4·69–16·64 mEq. per hour). In the two normal subjects a 10 mg. dose did not significantly increase the sodium and chloride excretion over that of a 7·5 mg. dose (fig. 2). The times of maximum water diuresis and maximum excretion of sodium and chloride were closely related (fig. 3).

Potassium Excretion

Potassium excretion was increased, but to a lesser extent than that of sodium and chloride. The mean increase was about twofold with the 5 mg. dose (1·89–2·63 mEq. per hour), and no further appreciable increase accompanied doses of 7·5 mg. or 10 mg. either in œdematous patients or normal subjects (table I, fig. 2).

Inorganic Phosphorus

The urinary excretion of phosphorus did not vary significantly in thirteen patients studied.

Blood Changes

The plasma levels of sodium, chloride, and urea before and after a single dose of bendrofluazide showed no significant change. The plasma-potassium level fell slightly (table I) in most of the patients studied after a single 7·5 mg. dose of bendrofluazide, and statistical analysis showed that the mean difference was significant at a 5% level ($t=2·59$, with 8 degrees of freedom; $P<0·05$).

In none of the seven œdematous patients who had several doses of bendrofluazide for periods of 8–25 days was the plasma-potassium level significantly altered

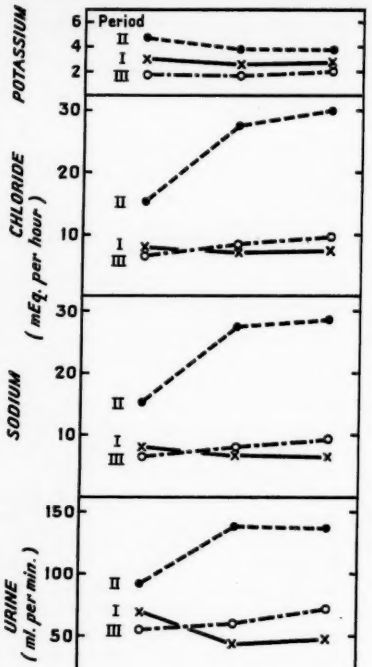


Fig. 2—Effect of doses of 5 mg., 7·5 mg., and 10 mg. of bendrofluazide on urine flow and electrolyte excretion (average of results in two normal subjects).

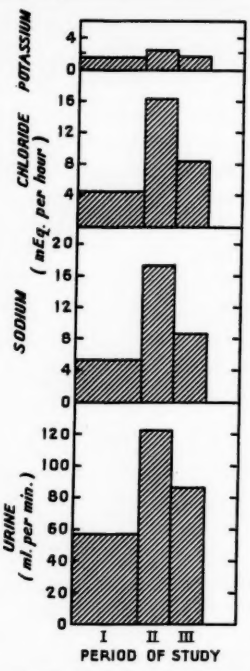


Fig. 3—Urinary volume and electrolyte excretion 24 hours before (period I), 0-12 hours after (period II), and 12-24 hours after (period III) 7·5 mg. bendrofluazide (mean values of 9 experiments).

(table II). One of these patients (case 15) was given a small potassium supplement (a total of 5 g. potassium chloride) at the start of bendrofluazide treatment; no supplement was given to the others.

Toxic Effects

No toxic effects were noted in any patient.

Discussion

The trial undoubtedly shows that bendrofluazide is an effective oral diuretic in various conditions causing œdema. Weight for weight it is much more potent than other benzothiadiazine derivatives so far described. 7·5 mg. of bendrofluazide seems to be as active as 2 g. of chlorothiazide, 200 mg. of hydrochlorothiazide, or 200 mg. of hydroflumethiazide. Our studies in the two normal subjects suggest that 7·5 mg. is the optimum dose of bendrofluazide for people of average body-weight.

The mode of action seems to be similar to that of other chlorothiazide derivatives—namely, an increased urinary excretion of sodium and chloride which causes a brisk osmotic diuresis. Bendrofluazide acts mainly in the first 12 hours after administration, but in a few cases the action is rather more prolonged.

Bendrofluazide, like other benzothiadiazine derivatives, causes an increased urinary excretion of potassium, but the loss is less than that of sodium and chloride. In several of the patients studied the plasma-potassium level fell slightly 24 hours after bendrofluazide was given. Probably this slight fall is often only temporary, because we observed no significant alteration in the plasma-potassium level in several patients with congestive cardiac failure, who had bendrofluazide twice or thrice weekly until they became free from œdema. It seems, therefore, that the risk of hypokalæmia is not great; but, as with other benzothiadiazine derivatives (Kennedy 1960), it is probably desirable to give a potassium supplement if long-term therapy is required, or if the patient has hepatic cirrhosis.

Summary

The biochemistry and urinary volume was studied in detail in fourteen œdematous patients before and after a single dose of bendrofluazide. Similar studies were made in two healthy young men after increasing doses of bendrofluazide. The plasma-potassium was determined before and after several doses of bendrofluazide in seven œdematous patients.

Bendrofluazide is a powerful oral diuretic, acting by increasing the excretion of sodium and chloride, which causes osmotic diuresis. The optimum dosage for most patients is probably 7·5 mg., but some will respond well to 5 mg., while a few may require 10 mg.

The urinary excretion of potassium is increased by bendrofluazide, but less than is that of sodium and chloride. The plasma-potassium level may fall slightly 24 hours after a single dose of bendrofluazide; but hypokalæmia was not observed in several patients with congestive cardiac failure who had the drug twice or thrice weekly for 8–25 days, with a satisfactory clinical effect.

No toxic effects were noted.

We wish to thank Prof. L. J. Davis for encouragement throughout this study. Bendrofluazide ('Aprinox') was supplied by Boots Pure Drug Co., Ltd.

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INHIBITION OF CHOLESTEROL BIOSYNTHESIS BY FARNESOIC ACID AND ITS ANALOGUES

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ACCORDING to one of the principal hypotheses concerning the pathogenesis of atherosclerosis, a high level of plasma-cholesterol is one of the initiating factors. Cholesterol is continuously synthesised in the body (Schoenheimer 1946) as well as being supplied in the diet

3 acetyl-coenzyme A
↓
Acetoacetyl-coenzyme A + acetyl-coenzyme A
↓
3-hydroxy-3-methylglutaryl-coenzyme A
↓
Mevalonic acid
↓
5-phosphomevalonic acid
↓
5-diphosphomevalonic acid
↓
Isopentenyl-pyrophosphate
↓
3,3-dimethylallyl-pyrophosphate
↓
Geranyl-pyrophosphate → geranic acid
↓
Farnesyl-pyrophosphate → farnesoic acid
↓
Squalene
↓
Lanosterol
↓
Cholesterol

Fig. 1—Intermediates in biosynthesis of cholesterol.

of all but the strictest vegetarians, and it accumulates in the body whenever the supply (endogenous synthesis plus dietary content) is greater than elimination by degradation.

If excess of cholesterol is a cause factor in initiating human atherosclerosis—and there is as yet no proof of this—lowering the cholesterol content of the body might be a desirable preventive or therapeutic measure. From the known facts of cholesterol metabolism, one might attempt to decrease the cholesterol content of the body in three general ways: (1) by inhibition of absorption from the intestine, (2) by stimulation of elimination, or (3) by inhibition of endogenous synthesis. The experiments we report are related to the last possibility.

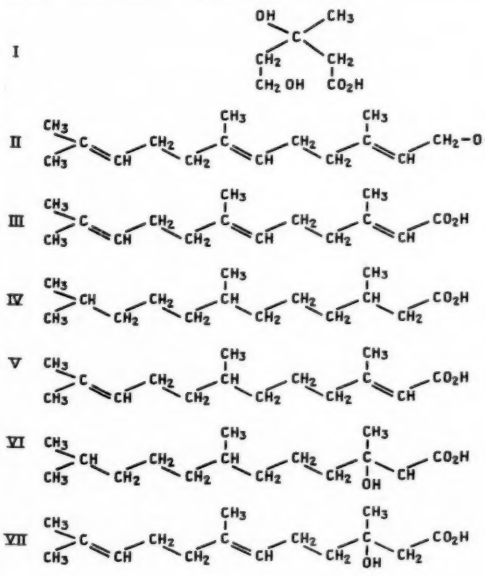

Fig. 2—Formulæ of intermediate compounds of cholesterol biosynthesis and of related substances.

The biosynthesis of cholesterol is one of the most complex biological processes yet revealed. The chain of reactions in its formation is summarised in fig. 1.

The early parts of this chain, preceding the formation of squalene, were elucidated after the discovery of mevalonic acid (fig. 2 I) in 1956 (for review see Popják and Cornforth 1960) by research-workers at the Merck Sharp & Dohme Research Laboratories, New Jersey, U.S.A. (see Folkers et al. 1959).

Theoretically one could inhibit cholesterol synthesis by interfering with any one reaction in the long synthetic chain. But it seems undesirable to interfere with the reactions preceding the formation of mevalonic acid, since acetyl-coenzyme A, acetoacetyl-coenzyme A, and 3-hydroxy-3-methylglutaryl-coenzyme A are also involved in metabolic reactions other than the synthesis of cholesterol. Beyond the stage of mevalonic acid, on the other hand, interference would cause more specific inhibition of sterol biosynthesis; for the only metabolic process, other than the biosynthesis of sterol, in which mevalonic acid is known to be involved in animals is the synthesis of the side-chain of ubiquinone—i.e., coenzyme Q (Gloor and Wiss 1958, Dialameh and Olson 1959).

During investigation of the biosynthesis of cholesterol in liver-enzyme preparations, some of the intermediates—but mainly farnesyl pyrophosphate (fig. 2 II)—were found to be metabolised by liver enzymes on an alternative pathway to carboxylic acids—e.g., to farnesoic (*trans-trans*-3,7,11-trimethyldodeca-2,6,10-trienoic) acid (fig. 2 III); Popják Horning, Bucher, and Cornforth 1959, Popják 1959). These carboxylic acids, of which farnesoic acid is only one, are not intermediates in cholesterol biosynthesis. On the contrary, they represent part of a pathway for the catabolic disposal of intermediates, like farnesyl pyrophosphate, and they also inhibit the utilisation of intermediates of cholesterol synthesis; hence they may be part of a physiological controlling mechanism. Although Dituri et al. (1957) reported that farnesoic acid was incorporated into cholesterol, this could not be confirmed in our laboratory (N. L. R. Bucher, M. Horning, and G. Popják; unpublished observations). The inhibitory action of farnesoic acid on the synthesis of cholesterol from mevalonate in vitro was first described by Wright and Cleland (1957), and we readily confirmed this observation. It was then a logical step to test analogues of farnesoic acid for their effect on cholesterol synthesis, in the hope that some might prove more powerful inhibitors than farnesoic acid itself.

One of us (G. P.) discussed these problems with members of the Merck Sharp & Dohme research laboratories during a visit to New Jersey in the summer of 1958. The Merck organisation group included Dr. Karl Folkers' research team, which discovered mevalonic acid, a key intermediate in sterol biosynthesis. The Merck group were already working on analogues of farnesoic acid as possible inhibitors of cholesterol synthesis, although the exact relation of farnesoic acid to sterol biosynthesis was not known at that time. Later Dr. Folkers, Dr. Sprague, and Dr. Bolhofer provided us with five substances (see fig. 2): 3,7,11-trimethyldodecanoic acid (IV); 3,7,11-trimethyldodeca-2,10-dienoic acid (V); 3-hydroxy-3,7,11-trimethyldodecanoic acid (VI); 3-hydroxy-3,7,11-trimethyldodeca-6,10-dienoic acid (VII); and 3,7,11-trimethyldodec-2-enoic acid (VIII). We had previously made the first of these compounds (IV) by catalytic hydrogenation of farnesoic acid, and this has been described in detail, together with the synthesis of farnesoic acid (Popják and Cornforth 1960). The chemical synthesis and characterisation of the compounds sent to

us by Dr. Folkers will be reported shortly. The chemical relation of compounds IV–VIII to farnesoic acid is evident from their formulæ. All these acids were tested for their ability to inhibit the biosynthesis of cholesterol from mevalonate in liver-enzyme preparations.

Methods

Homogenates of rat liver were prepared as described by Bucher and McGarrahan (1956) in 0·1 *M* potassium-hydrogen-phosphate buffer, pH 7·4, containing 0·005 *M* $MgCl_2$ and 0·03 *M* nicotinamide. The homogenates were centrifuged at 10,000 *g* for 25 minutes to sediment the unbroken cells, nuclei, and mitochondria. The supernatants (S_{10} preparations) of the centrifuged homogenates, which were shown to synthesise cholesterol from mevalonic acid, were used as previously described (Popják et al. 1958). For each test 5 ml. incubations were set up containing 4 ml. of S_{10}, to which was added 2 μmoles each of reduced diphosphopyridine nucleotide and triphosphopyridine nucleotide, 5 μmoles of adenosine triphosphate (A.T.P.), and 2 μmoles of DL−[2−^{14}C] mevalonate. The test substances, as potassium salts, were added to the incubations in concentrations of $0·2\times10^{-3}$ *M* to 2×10^{-3} *M*. The reaction mixtures were incubated aerobically at 37°C for 2 hours, after which they were hydrolysed with 2*N* KOH. The unsaponifiable substances were extracted with light petroleum and cholesterol (and other 3β-hydroxysterols) precipitated as the digitonide and prepared for radioactive counting as described by Popják et al. (1958). From the known specific activity of the [2−^{14}C] mevalonate (0·2 μC per μmole), and from the radioactivity of the isolated sterol-digitonides, could be calculated the number of micromoles of mevalonate converted into sterol. Two types of control were used: one contained only the components of the enzyme system with its coenzymes, the other contained potassium dodecanoate (laurate) to guard against the possibility that the effect of the various substances was only that of a soap.

In addition to this complete enzyme system we also tested the effects of compounds IV–VII and of farnesol on purified liver mevalonic kinase. In experiments with this enzyme we used the standard spectrophotometric assay described by Levy and Popják (1959, 1960) for liver mevalonic kinase. This assay measures the rate of phosphorylation of mevalonic acid (μmoles per min. per mg. protein). The enzyme preparation which we used phosphorylated 1·2 μmoles of mevalonate per min. per mg. protein at 37°C in the absence of an inhibitor. In our experiments the rate of phosphorylation of mevalonate in the presence of an inhibitor was compared with the rate observed in the control.

In the spectrophotometric assay of mevalonic kinase the formation of adenosine diphosphate (A.D.P.) from A.T.P. during phosphorylation of mevalonate is measured with the aid of pyruvic kinase and lactic dehydrogenase according to the following reactions (1), (2), and (3):

1. Mevalonate + A.T.P. $\xrightarrow{\text{mevalonic kinase}}$ 5-phosphomevalonate + A.D.P.
2. A.D.P. + phosphoenolpyruvate $\xrightarrow{\text{pyruvic kinase}}$ pyruvic acid + A.T.P.
3. Pyruvic acid + D.P.N.H. $\xrightarrow{\text{lactic dehydrogenase}}$ lactic acid + D.P.N.

We ascertained that the substances tested had no effect on reactions (2) and (3).

TABLE I—INHIBITION OF CHOLESTEROL BIOSYNTHESIS IN VITRO BY FARNESOIC ACID AND ITS ANALOGUES

All experiments were made under identical conditions (see text) except that a different enzyme preparation was used in each.

Experiment no.	Substance added, with concentration (m/molar)	Mevalonate converted into cholesterol (μmoles)	% inhibition
1	None, control	0·370	0
	IV 0·2	0·240	35
	IV 0·4	0·170	54
	IV 1·0	0·002	>99
	IV 2·0	0·000	100
	V 0·2	0·380	0
	V 0·4	0·082	78
	V 1·0	0·000	100
	V 2·0	0·000	100
2	None, control	0·630	0
	Potassium laurate, 1·0	0·640	0
	VI 0·2	0·480	24
	VI 0·4	0·055	91
	VI 1·0	0·000	100
	VII 0·2	0·305	52
	VII 0·4	0·098	85
	VII 1·0	0·000	100
3*	None, control	0·408	..
	VIII 0·2	0·607	..
	VIII 0·4	0·577	..
	VIII 1·0	0·496	..
	Potassium laurate, 0·4	0·557	..
	1·0	0·563	..
4	None, control	0·509	..
	None, control	0·525	..
	IV 0·2	0·310	40
	IV 0·4	0·044	91
	IV 1·0	0·000	100
	III 0·2	0·437	16
	III 0·4	0·375	28
	III 1·0	0·357	31

* This experiment was repeated with identical results.

TABLE II—EFFECTS OF ANALOGUES OF FARNESOIC ACID ON PURIFIED LIVER MEVALONIC KINASE

The test system was the standard spectrophotometric assay (Levy and Popják 1959, 1960) for liver mevalonic kinase. The enzyme used phosphorylated, in the absence of an inhibitor, 1·2 μmoles of mevalonate per min. per mg. protein. All substances tested were added in 1 millimolar (= 1 μmole per ml.) final concentration.

Substance	% inhibition
IV	94·8
V	40·7
VI	76·5
VII	31·0
Farnesol	0

Results and Discussion

Our results (table I) showed that all the substances tested, except compound VIII and potassium laurate, inhibited cholesterol synthesis very strongly. The action of farnesoate compared with that of its analogues (IV–VII) was feeble; substantial inhibitions (80–90%) could be achieved with farnesoate only at higher concentrations ($10\times10^{-3}M$). The fact that compound VIII and potassium dodecanoate had no inhibitory action, and even stimulated slightly the conversion of mevalonate into cholesterol, suggests that the effect of the other substances is specific.

The mechanism of action of compounds IV–VII is not known in detail. So far we have investigated their effect on only one of the enzymes—mevalonic kinase—involved in the chain of biosynthesis (see fig. 1). Mevalonic kinase (Tchen 1958, Levy and Popják 1959, 1960) is the enzyme responsible for the first transformation of mevalonic acid, the product of its action being 5-phosphomevalonate. It has already been reported (Levy and Popják 1960) that compound IV strongly inhibited mevalonic kinase. Further tests made in collaboration with Dr. Levy showed that compounds V, VI, and VII also inhibited mevalonic kinase, but not as strongly as did compound IV. The results of the experiments with purified mevalonic kinase are summarised in table II. Only compound IV showed powers of inhibiting mevalonic kinase comparable to those found in the complete cholesterol-synthesising system. This suggests that compounds V, VI, and VII act also on reactions of the synthetic chain beyond that catalysed by mevalonic kinase.

The results of the experiments with the analogues of farnesoic acid in vitro, encouraged us to test them also in vivo, but as yet we have no information about their effects in animals.

Summary

Analogues of farnesoic acid (*trans-trans*-3,7,11-trimethyldodeca-2,6,10-trienoic acid) were tested for their effects on the biosynthesis of cholesterol from mevalonate in liver-enzyme preparations.

Four substances—3,7,11-trimethyldodecanoate; 3,7,11-trimethyldodeca-2,10-dienoate; 3-hydroxy-3,7,11-trimethyldodecanoate; and 3-hydroxy-3,7,11-trimethyldodeca-6,10-dienoate—in concentrations of 1 m*M* (1 μmole per ml.) abolished completely the synthesis of cholesterol from mevalonate. A fifth substance—3,7,11-trimethyldodec-2-enoate—had no inhibitory action. The active substances were far more potent inhibitors than was farnesoic acid.

The effect of 3,7,11-trimethyldodecanoate may be attributed almost entirely to its inhibition of mevalonic kinase. Although the other three inhibitors affected mevalonic kinase, they probably also act on reactions catalysed by other enzymes in the biosynthetic chain of cholesterol.

Testing the inhibitors of cholesterol biosynthesis in vivo seems to be justified because they may lower body cholesterol levels by decreasing endogenous synthesis.

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GENITAL LISTERIOSIS AS A CAUSE OF REPEATED ABORTION

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REPEATED abortion is seldom satisfactorily explained; and the distressing inability to offer any real help in these cases prompted us to seek a new approach. We found that a hitherto unknown form of human listeriosis—genital listeriosis—is an important cause of abortion and repeated abortion. By genital listeriosis we mean a state of chronic infection of the genital organs of apparently healthy women by listeria microorganisms. It manifests itself by the continuous excretion of microorganisms from the uterine cervix over long periods, and by abortion or premature stillbirth in supervening pregnancies.

Microorganisms belonging to the genus listeria were first isolated from animals by Murray et al. (1926) and by Pirie (1927). Nyfeldt (1929) was the first to isolate listeria from a human case. Murray (1955) stated that microorganisms belonging to the genus listeria were isolated from 27 species of animals in 26 countries all over the globe, among them Israel. Their pathogenicity for humans has been proved beyond doubt, for listeria microorganisms have been isolated from a variety of diseases, such as meningitis, infectious mononucleosis, pneumonia, endocarditis, granulomatosis infantiseptica (Potel 1951, 1952), &c.

It is known (Murray et al. 1926, Gray 1958, Schultz 1957, Suchanova et al. 1958, Young and Firehammer 1958, Gray et al. 1955) that listeriosis causes abortion in wild and domestic animals; so in the case of a 37-year-old woman with a history of three consecutive unexplained abortions over a period of two years, we looked for listeria organisms. We cultured swabs from cervical and vaginal secretions and the cultures were repeatedly positive (twelve times in four months). In fact listeriosis has been lately suspected to cause habitual abortion in the human (Seeliger and Cherry 1957, Rost et al. 1958), but this opinion has either not been accepted (Potel and Alex 1956) or flatly rejected.

Reviews by Gray et al. (1957), Seeliger and Cherry (1957), Krepler and Flamm (1956), and Hoeprich (1958) record considerable progress in the investigation of the bacteriological, serological, and clinical aspects of listeriosis. Nevertheless, it is apparent that research in this rapidly expanding subject is still at its beginning. The main cause of this lag is the great difficulty encountered in primary isolation of listeria from pathological material.

Following our first success, investigation was conducted in two directions:

(1) The development of a simple and rapid method for the primary culturing of these microorganisms.

(2) A search for listeria in a large series of cases of repeated abortions.

Material and Methods

Material for cultures was obtained from the cervical secretion with sterile swabs. The swabs were kept in the refrigerator until cultured. The culture medium was prepared as follows:

The following ingredients were dissolved in 1000 ml. of distilled water and autoclaved for fifteen minutes at 15 lb. pressure:

Bacto tryptose	20 g.
Bacto beef extract	3 g.
Sodium chloride	5 g.
Dextrose	1 g.
Bacto agar	20 g.

Just before pouring the plates, 1 ml. of 0·5% sterile solution of vitamin B_1 (aneurine HCl *B.P.*) in distilled water was added. The final pH was 6·7–6·8.

The plates were incubated at 37°C for twenty-four hours to test for sterility, then they were directly streaked from the swabs rich in cervical secretion, and incubated in candle jars at 37°C for twenty-four hours. The agar plates were then examined for the characteristic type of growth—e.g., small round colonies (Gray et al. 1957). Microscopic smears from these colonies were considered positive on finding typical gram-positive rods as described by Gray et al. (1957). The strains from all cases were kept in stab cultures for further investigation and storage. Some of these strains were sent to Dr. H. P. R. Seeliger in Bonn, Germany, for typing. The strains that arrived alive were typed *Listeria monocytogenes* 4b (Seeliger 1959).

Within a period of five months we examined 34 women with a history of repeated abortion. Of these, 25 were positive, i.e., listeria microorganisms were isolated at least three times from material taken at one to five days' intervals. Pregnant women with two positive cultures at one-day interval were considered positive, since treatment had to be started immediately for obvious reasons.

87 controls (women of reproductive age, married or unmarried, healthy or affected by irrelevant gynæcological conditions, such as dysmenorrhœa, amenorrhœa, genital prolapse, stress incontinence, &c.), were examined for listeria. None of the controls had a history of abortions.

* Professor Rappaport died on July 17, 1959, and his coauthors acknowledge his invaluable cooperation, which was interrupted by his illness. He was not responsible for the final conclusions reached in this paper.

Results

The 25 positive cases (table I) fall into three groups:

Group 1 includes 3 women, from whom listeria were isolated in the second trimester of their pregnancy and who aborted shortly afterwards. In case 1 listeria were isolated from the amniotic fluid of the aborted pregnancy.

Group 2 comprises 8 women from whom listeria were isolated during the first trimester of pregnancy (case 4 during the second trimester). They received treatment and their pregnancies proceed regularly.

Group 3 comprises 14 women from whom listeria microorganisms were isolated when non-pregnant.

All these women had 1 to 6 abortions in periods of time up to eight years. The period during which they were positive to listeria, from the first positive culture until cultures became negative after treatment, was up to twenty weeks.

None of the positive women had any complaints, with the exception of case 2 (group 3), who suffered from vaginal discharge and itching. It is worth mentioning that listeria could be isolated in this case only after trichomonas infection was cleared.

In 3 of the 9 negative cases (table II) abortions could be attributed to other causes. Most of these patients were examined at the beginning of the investigation, and they are being studied again by our standard method.

None of the 87 control women harboured listeria in their genital organs.

The following case (case 5, group 3) deserves special mention.

A 24-year-old had a history of (1) stillbirth at 7th month; (2) missed abortion at 6th month; (3) stillbirth at 7th month; (4) missed abortion at 5th month, all in the course of 5 years. She was referred to us for investigation eight months after her last abortion and *Listeria monocytogenes* was isolated from her cervical secretion. She disappeared and came back four months later with a missed abortion. The ovum was expelled whole and listeria were cultivated from the liquor amnii. The macerated fœtus was 13 cm. long.

The earliest fœtus reported in the literature from which listeria microorganisms were isolated was described by Stark (1953): it was 25 cm. long, in the fifth month of pregnancy.

Seeliger (1957), a leading authority on listeriosis, writes: "Unfortunately, bacteriology does not give us the answer in all cases, particularly in those cases where the diagnosis is suspected but Listeria cannot be cultivated. . . . Up to now, no one has succeeded in isolating *Listeria monocytogenes* from pregnant women before the disease is manifest in the newborn . . ."[11] He still holds this opinion.

TABLE II—REPEATED ABORTION NEGATIVE TO LISTERIA

No.	Age (yr.)	No. of pregnancies preceding examination	No. of live births exc. neonatal deaths	No. of abortions (and stillbirths or neonatal deaths)	No. of negative cultures	Observations
1	24	2	..	1 (1)	1	..
2	24	6	..	3 (2)	4	1 artificial abortion. Incompetence of internal os
3	23	7	..	7	5	Very early abortions. The husband has oligospermia, hypokinesis
4	27	5	1	4	3	..
5	34	5	1	4	2	Very early abortions. The husband has oligospermia, hypokinesis
6	30	4	..	2 (2)	1	..
7	28	5	3	2	3	..
8	36	3	..	1 (2)	1	..
9	35	4	1	2 (1)	3	..

Treatment

All the pregnant women in group 2 (table I) are now under treatment. Treatment was started immediately the infection was proved. 11 out of 14 non-pregnant women of group 3 are under treatment as well, to enable them to become pregnant without undue risk of abortion.

Treatment generally consisted of large doses of penicillin (1 million units daily for fourteen days) and sulphamethoxypyridazine ('Lederkyn') 1 g. daily for fourteen days. In most cases the cervical cultures became negative after five or six days. As we found that cultures became positive again one to six weeks after stopping treatment, we believe that maintenance doses of sulphamethoxypyridazine (0·5 g. daily) should be continued for long

TABLE I—REPEATED ABORTION DUE TO GENITAL LISTERIOSIS

—	Case	Age (yr.)	No. of pregnancies preceding diagnosis	No. of live births exc. neonatal deaths	No. of abortions (and stillbirths or neonatal deaths)	Month of pregnancy when listeria diagnosed	No. of positive cultures	Duration of positivity (weeks)	Presumed minimal duration of infection	Observations
Group 1	1	22	3	..	2 (1)	6th	1	..	3 yr.	Listeria isolated from cervix. 5 days later aborted. Listeria isolated from amniotic fluid. After abortion, cervical secretion negative for 2 months.
	2	33	6	1	4 (1)	6th	1	..	?	Aborted in the 6th month. Then negative for 2 weeks
	3	25	1	..	1	4th	1	..	3½ yr.	Aborted in the 4th month. Then negative during 3 weeks. Again positive after 1 month.
Group 2	1	32	8	2	1 (3)	2nd	5	18	14 yr.	Now pregnant 7th mo. 2 artificial abortions.
	2	22	2	..	1 (1)	2nd	4	10	2 yr.	" " 6th "
	3	35	8	5	3	3rd	4	10	1½ yr.	" " 6th "
	4	32	5	1	4	5th	2	1	8 yr.	" " 5th "
	5	26	3	..	3	3rd	2	1	2½ yr.	" " 5th "
	6	41	5	2	3	2nd	5	5	5 yr.	" " 4th "
	7	30	3	1	2	2nd	2	1	3 yr.	" " 3rd "
	8	33	4	..	4	1st	2	1	6 yr.	" " 3rd "
Group 3	1	37	5	2	2 (1)	..	12	18	2 yr.	..
	2	32	3	1	2	..	11	18	2½ yr.	..
	3	23	2	..	2	..	15	20	2 yr.	..
	4	25	6	3	2	..	6	20	1½ yr.	1 artificial abortion
	5	24	5	..	3 (2)	..	1	..	5 yr.	Positive before last pregnancy, then aborted at 4th month. Listeria isolated from amniotic fluid
	6	34	6	..	4	..	4	8	5 yr.	..
	7	33	7	1	6	..	7	14	8 yr.	..
	8	25	1	..	1	..	4	10	4 mos.	..
	9	26	4	1	2	..	4	6	16 mos.	1 artificial abortion
	10	22	3	1	2	..	4	7	1 yr.	..
	11	27	3	1	2	..	3	1	1½ yr.	..
	12	23	2	..	2	..	3	3	9 mos.	..
	13	27	2	..	2	..	3	1	7 mos.	..
	14	30	4	..	3	..	3	1	2 yr.	1 artificial abortion

periods. This is our policy at present. Our short experience with treatment does not allow us to say more. It is noteworthy that all the pregnant patients under treatment are well and their pregnancies are proceeding normally.

Summary

A relationship between listeria microorganisms and repeated abortion has been proved. Listeria were isolated from the genital organs of 25 out of 34 women with a history of repeated abortion. Listeria microorganisms were also isolated from aborted products of conception.

Genital listeriosis has been described as a state of chronic listeria infection of the genital organs of apparently healthy women. Genital listeriosis manifests itself by the continuous excretion of organisms from the uterine cervix over long periods and by abortion or premature stillbirth in supervening pregnancies.

Pregnant women affected by genital listeriosis have not so far aborted after treatment with penicillin and sulphamethoxypyridazine.

We are indebted to Dr. H. P. R. Seeliger, of the Institute of Hygiene, University of Bonn, Germany, for his identification of cultures. We wish to thank Prof. Joseph Asherman for referring to us many of his patients for diagnosis and treatment. We are grateful to the American Cyanamid Co., Lederle Laboratories Division, for the supply of ' Lederkyn ' for this investigation.

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EPIDEMIC CERVICAL MYALGIA

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ACUTE cervical myalgia " stiff neck " is fairly common; and its true incidence is probably even greater than is generally appreciated, because many sufferers do not trouble their doctors with symptoms that are familiar and usually short-lived.

The ætiology is unknown. Patients usually attribute their symptoms to the effects of draughts; while their doctors often invoke that ill-defined condition—" fibrositis "—to explain the illness. Infection does not seem to have been suggested as a cause until Massell and Solomon (1935) and, later, Beeson and Scott (1941, 1942) concluded, from retrospective surveys based on questionaries answered by patients, that acute " stiff neck " could occur in epidemic form. Subsequently, other outbreaks of acute myalgia, principally affecting the trapezius muscles, were described by Copeman (1944) and Wilson (1946). All these workers agreed that epidemic " stiff neck " was probably an infection, possibly due to a virus, and that clinically the condition was distinct from Bornholm disease. Beeson and Scott (1941, 1942) tried to transmit the disease to volunteers, using throat washings and/or blood taken from affected patients. Throat washings had no apparent effect; but inoculation with blood appeared to produce the disease in some volunteers, though the evidence was not conclusive. Attempts to infect laboratory animals and developing chick embryos failed.

Present Investigation

In the autumn of 1958 and again in the late summer of 1959 a small epidemic of acute myalgia, principally affecting the trapezius muscles, occurred among nurses at this hospital. In all, 13 nurses reported sick—7 in the first epidemic and 6 in the second. The total nursing staff at the main hospital numbers about 725, so the attack-rate seems very small. Inquiries among the nurses suggests, however, that many others were affected during the relevant periods but did not consider their symptoms severe enough to seek medical advice.

All except 1 of the 13 nurses who reported sick were admitted, and the condition was studied more fully than appears to have been possible before.

CASE-RECORDS

Case 1.—A 21-year-old nurse was admitted on Aug. 7, 1958. For a day she had had severe pain in the neck which began suddenly and was aggravated by movement. She was in considerable pain and held her neck flexed to the right. Though there was no true neck stiffness, all movements were restricted by pain. Both trapezius muscles were extremely tender to palpation over most of their extent, but there were no other abnormal physical signs and she was afebrile.

Progress.—After admission there was slight intermittent pyrexia, of up to 99·6° F, for four days. The pain in her neck gradually abated, but six days after admission aching pain developed in both hands and both knees unaccompanied by stiffness or swelling. These symptoms disappeared within twenty-four hours, and thereafter she was quite well.

Case 4.—A 20-year-old nurse was admitted on Sept. 8, 1958. That morning she had suddenly experienced very severe interscapular pain spreading to both scapular regions, aggravated by movement and breathing. She was in severe pain. Though there was no true neck stiffness all movements were restricted by pain, and both trapezius muscles were very tender to palpation. There were no other abnormal physical signs and she was afebrile.

Progress.—The pain in the neck remained severe for nine days, after which it gradually subsided. Seven days after admission the patient complained of pain in both knees and both ankles which lasted for four days; there was no associated swelling or restriction of movement. The patient remained in hospital for twelve days, and from the fourth day until discharge there was intermittent pyrexia of up to 100°F. On discharge she was symptom-free.

Case 9.—A 20-year-old nurse was admitted on Aug. 3, 1959. For one day she had had vague abdominal aching and nausea. On the day of admission aching developed in the neck, lower back, and legs. She was afebrile. There was severe tenderness of both trapezius muscles, but no other abnormal physical signs.

Progress.—A few hours after admission the patient's temperature rose to 101°F, but later on the same day it fell to normal again and remained so until the sixth day when it rose to 99°F. She was discharged on sick leave, apparently cured, eight days after admission, but the following day she was readmitted because of generalised muscular aches, headache, and neck stiffness which had made her family doctor suspect poliomyelitis. Lumbar puncture was now carried out, but the cerebrospinal fluid was normal in all respects. After a further nine days, during which she complained of transient fleeting muscular pains, she recovered completely. Throughout the second admission she was afebrile.

Case 11.—A 22-year-old nurse was admitted on Aug. 6, 1959. For two days she had had generalised muscular aching, and on the day before admission occipital headache, mild photophobia, and pain in the neck. There was slight photophobia and severe tenderness of both trapezius muscles. There was no true neck stiffness, though all movements were restricted by pain. No other abnormal physical signs were found, and the patient was afebrile.

Progress.—The day after admission severe trismus developed; this persisted for three days and then passed off. This symptom was severe enough for tetanus to be suspected, particularly as there was a history of a small abrasion of the hand ten days before. When the trismus passed off, the patient was quite well.

The remaining cases are summarised in the accompanying table.

INVESTIGATIONS

White-blood-cell counts were carried out in 11 of the 13 cases, and in 10 the total and differential counts were within normal limits. In 1 case there was leucopenia (2,200 per c.mm.) with a normal differential count, and in this and 1 other case a few typical lymphocytes were seen, but Paul Bunnell tests were negative.

The erythrocyte-sedimentation rate (Westergren) was measured in 10 cases; in 8 it was normal, and in 2 it was raised (25 and 27 mm. in the first hour).

In 2 of the cases seen in 1958 specimens of stool collected within five days of the onset of symptoms were examined for the presence of Coxsackie viruses, by inoculation into suckling mice, with negative results.

In 4 of the 1959 cases specimens of stool collected within five days of the onset of symptoms were examined for the presence of Coxsackie-B virus, adenovirus, poliomyelitis virus, or other cytopathogenic agents, by inoculation into Hela cell cultures; the results were negative. In five cases complement-fixation tests on paired sera showed no evidence of recent infection with *Rickettsia burneti* or the following viruses: influenza (A, B, C), parainfluenza 1 (Sendai), mumps, adenovirus, and psittacosis. Streptococcal M.G. agglutination tests were also negative in all 5 cases. Monkey-kidney tissue-culture neutralisation tests on the sera showed no evidence of infection with Coxsackie viruses B types 1–5.

Discussion

In the epidemic illness described here the outstanding feature was the pain and tenderness affecting the trapezius muscles. In 11 cases this was bilateral, and in 2 unilateral; its time of onset during the illness was inconstant.

Other symptoms included mild transient aches in various muscles and joints in 10 patients, occipital headache in 5, dizziness in 2, pain in the masseter muscles in 2 (1 of whom had severe trismus), and colicky abdominal pain and nausea in 1. The illness lasted on an average for nine days; there was no evidence of inflammation of the throat or enlargement of cervical glands; constitutional upset was slight; and in most cases fever was absent or slight and short-lasting.

The patients were all student nurses who shared the same dining-room with many others, but they did not all work in one particular department or ward or live in close proximity to one another.

When the first patient presented with pain in the neck as the only symptom, its severity suggested a local spinal lesion; but the diffuse tenderness of both trapezius muscles, and later the onset of fever, and aches and pains elsewhere, pointed to some generalised disturbance, possibly a virus infection.

In cases 2 and 3 pain in the neck was a late symptom, and initially the vague malaise and muscle and joint pains raised the possibility of influenza, or of mild acute rheumatism even though the affected joints were not swollen. The absence of fever, however, was against either of these diagnoses, and in both patients acute rheumatism seemed even less likely when the erythrocyte-sedimentation rate proved to be normal.

In some of the other cases the combination of muscular aching, headache, and neck pain presented a picture difficult to distinguish with certainty from pre-paralytic poliomyelitis; and indeed this diagnosis was seriously

DATA ON 9 PATIENTS

Case no.	Age (yr.)	Date admitted	Symptoms	Signs	Length of illness (days)
2	22	Aug. 27, 1958	3 days vague malaise and slight aching in masseter muscles; 1 day pain in right knee and ankle; 1 day after admission giddiness; 6 days after admission pain in neck and shoulders, left wrist, and knee lasting 2 days	None on admission; 6 days later severe tenderness of trapezius muscles; afebrile	12
3	19	Sept. 6, 1958	3 days pain and stiffness in both knees and wrists; later transient muscle and joint aches, trapezius muscles painful for 1 day	Tender proximal interphalangeal joints; later tenderness of trapezius muscles; afebrile	13
5	22	Sept. 10, 1958	2 days vague malaise, occipital headache, and pain in neck; 3 days after admission pain and stiffness in knees and wrists lasting 3 days	Severe tenderness of both trapezius muscles; temp. 99°F on two occasions	8
6	19	Sept. 12, 1958	Day of admission pain and stiffness of neck and occipital headache; 4 days later transient aching both knees	Severe tenderness both trapezius muscles; afebrile	6
7	23	Sept. 12, 1958	1 day general malaise; 4 days later pain and stiffness in neck	On admission temp. 102°F, falling to normal after a few hours, but rising to 100°F on 5th day when both trapezius muscles were tender for 2 days	8
8	23	July 29, 1959	7 days occipital headache and pain in neck and shoulders, pain lasting 9 days (previous attack: case 5)	Severe tenderness of both trapezius muscles; afebrile	16
10	19	Aug. 5, 1959	1 day shivering, aching in neck and legs; 2 days later pain and stiffness of neck	On admission temp. 101°F, then 99°F for 4 days; 2 days after admission tenderness of left trapezius muscle	5
12	19	Aug. 20, 1959	3 days severe pain in neck, gone when first seen	Slight tenderness of right trapezius muscle; afebrile	6
13	19	Aug. 26, 1959	1 day occipital headache and severe pain in neck, dizziness, and aching of legs	Severe tenderness of both trapezius muscles; afebrile	6

Cases 1, 4, 9, and 11 are described in the text.

entertained by another doctor who saw one of the patients (case 9) when she relapsed after discharge from hospital. But the absence of any true neck rigidity, and the fact that fever was usually absent at the onset of the illness, made poliomyelitis unlikely.

In a few patients the sudden onset of the muscular pain and its severity were reminiscent of Bornholm disease. In the classical form this disease is characterised by the sudden onset of severe pain in the chest or upper abdomen, usually aggravated by breathing and often by swallowing; moderate pyrexia; and a pleural rub. The illness may last for only a few days, or may run a lengthy or relapsing course.

Pain or tenderness in the trapezius muscles has occasionally been encountered in Bornholm disease (Sylvest 1934, Ronald 1942, Nichamin 1945); but, of the patients so affected, severe pain in the chest or upper abdomen was the presenting or outstanding feature in almost all, fever of 102–103°F was not infrequent, and the erythrocyte-sedimentation rate was commonly raised.

None of the patients described here had pain or tenderness in the chest or upper abdomen, only the trapezius muscles being affected to any significant degree. The temperature remained normal throughout the illness in 7 of the 13 cases, and rose above 100°F in only 4. The erythrocyte-sedimentation rate was raised in only 2 of the 8 patients in whom it was measured.

Thus there are several differences between this condition and classical Bornholm disease; and virological investigations did not support the latter diagnosis.

The epidemic illness described here is probably identical with that described by Massell and Solomon (1935), Beeson and Scott (1941, 1942), Copeman (1944), and Wilson (1946); and probably also with the condition described by Warin (1956) as a variant of Bornholm disease.

In all the cases described by these several workers, the clinical course of the illness did not differ significantly from that in present cases: fever was unusual; the blood count was usually within normal limits; and the erythrocyte-sedimentation rate was normal in all the cases in which it was estimated, except for the second of two outbreaks described by Copeman (1944) when it was found to be raised in all 8 patients.

In 5 patients of Beeson and Scott (1941, 1942), 1 patient of Copeman (1944), and 2 patients of Wilson (1946) persistent generalised "fibrositis" later developed. In the present series this complication was not seen, but 1 patient had a relapse a day after recovering from the first attack, and 1 other had attacks during both epidemics.

Conclusion

Epidemic "stiff neck" is an illness with features suggesting a virus infection, and it appears to be distinct from Bornholm disease.

Summary

Two outbreaks of epidemic "stiff neck"—epidemic myalgia principally affecting the trapezius muscles—are described.

The condition did not have the clinical features of classical Bornholm disease, not did virological studies support this diagnosis.

The illness had features suggesting a virus infection, but the causal organism was not discovered.

I am very grateful to Lord Evans, Dr. W. Tegner, Prof. C. F. Barwell, and Dr. F. O. MacCallum for helpful criticism and advice; and to Dr. S. E. Reed, of the London Hospital department of bacteriology, and Dr. D. R. Gamble and Dr. C. E. D. Taylor, of the Central Public Health Laboratories, Colindale, for the virological investigations.

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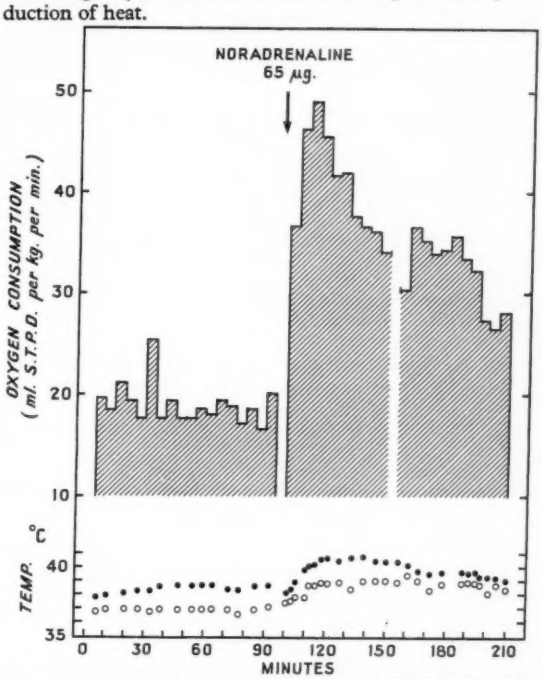
Preliminary Communication

POSSIBLE ROLE OF NORADRENALINE IN CONTROL OF HEAT PRODUCTION IN THE NEWBORN MAMMAL

ON the basis of our experiments using the unanæsthetised cat, rat, mouse, and rabbit, we are suggesting that noradrenaline is secreted by the neonate in response to a lowered environmental temperature. This noradrenaline raises the heat production of the animal and enables it to maintain its deep body-temperature.

We are, at this stage, offering evidence only on the effect of noradrenaline on general heat production, and have not attempted to integrate this with other effects it may have on the animal's economy or to suggest the site of its action. Shivering may also be involved to some degree in the production of heat.



Calorigenic effect of noradrenaline in an unanæsthetised 5-day-old, 151 g. kitten.

At the arrow the animal was removed briefly from the metabolism chamber for a subcutaneous injection of noradrenaline 400 μg. per kg. Environmental temperature was 35°C, and the animal was in an atmosphere of approximately 21% oxygen, 79% nitrogen. Temperatures were measured by thermocouples (closed circles, rectal; open circles, skin of back); and oxygen consumption, measured continuously, is plotted in the form of a 5 min. histogram. The break in the hatching indicates a two-minute interruption of the recording.

Observe the rapid increase in oxygen consumption and the less rapid rise in body-temperature. As all three values are rising together heat production must have increased.

METHODS

The evidence consists in observations mainly carried out on the newborn kitten but supported in all main particulars in the rat, mouse, and rabbit (the guineapig is somewhat atypical in that adrenaline is also calorigenic). The animals were studied at 30°C or 35°C environmental temperature, before and after a subcutaneous injection of a ganglion-blocking agent (hexamethonium iodide 10 mg. per kg. body-weight) and/or *l*-noradrenaline (400 μg. per kg.) or *l*-adrenaline (400 μg. per kg.). Measurements were made of oxygen consumption and rectal and skin temperature in individual unanæsthetised animals. Metabolism chambers of the Richards and Collison [1] pattern were used which allow continuous recording of oxygen consumption. Temperatures were measured from thermocouples inserted into the rectum and applied to the skin of the back and pad.[2] After a preliminary stabilisation period of about 80 min., the animal was removed, injected, and replaced and the observations continued.

RESULTS

The findings were as follows:

1. Hexamethonium at 30°C reduced heat production. The oxygen consumption falls rapidly, and this is *followed* by a fall in deep and surface temperatures. The reason for such an order of events must be a fall in heat production, not primarily an increase in heat *loss*.
2. Hexamethonium at 35°C had little effect on oxygen consumption and heat production.
3. Noradrenaline at 30°C had little effect in doses of 400 μg. per kg. in the normal kitten, but see (5) below.
4. Noradrenaline 400 μg. per kg. at 35°C increased oxygen consumption and heat production (see accompanying figure). The order of events and the rise in skin temperature show that a rise in oxidative heat production must precede the rise in body-temperature.[3]
5. Noradrenaline at 30°C reversed the changes set in motion by hexamethonium, but hexamethonium at 35°C did not prevent the rise in heat production caused by noradrenaline.
6. Subcutaneous adrenaline (400 μg. per kg.) or subcutaneous saline (0·9% sodium chloride, 4·0 ml. per kg.) had little or no action as thermogenic agents in the neonate.
7. Age altered the responses to both hexamethonium [4] and noradrenaline. Maximal effects were found in the first few days of life, and little action was observed by the age of 5–7 weeks in the cat and 3–4 weeks in the rat.

DISCUSSION

We interpret these findings as meaning that at 35°C there is little or no natural secretion of noradrenaline: the animal is in the so-called zone of thermal neutrality and its oxygen consumption is low. Hexamethonium is, under these circumstances, not preventing the release of noradrenaline, so blockade does not alter heat production. At 30°C however, there is normally some secretion of noradrenaline and the animal has a higher oxygen consumption and heat production. This rise of metabolism at a lower temperature is a well-known phenomenon. Consequently, at 30°C hexamethonium blockade will deprive the animal of its normal calorigenic stimulus, and heat production will fall.

Noradrenaline at 30°C will not be calorigenic unless the dose injected, and the amount absorbed from the injection site, is sufficient to raise the blood concentration above its existing level. Less than this will be "buffered" by a cutting down of normal secretion. This "buffering", however, is impossible if, on account of a high external temperature, no secretion is taking place. Therefore, at 35°C injected noradrenaline is calorigenic. Heat production and temperature gradients (deep body to environment) increase to values normally associated with a lower environmental temperature.

CONCLUSION

We feel that the most likely explanation of the results is that the neonate of some species normally depends upon the secretion of noradrenaline to keep it warm. It is interesting that noradrenaline should be cast in this role, as in the adult it is considerably less calorigenic than adrenaline.[5] Only in the experiments of Hsieh et al.[6 7] and Depocas [8] has the reverse been shown, and then only in the anæsthetised, cold-adapted adult rat. However, our results may perhaps point to a function for the large amount of chromaffin tissue known to be present in the newborn of many species, and its relatively high content of noradrenaline. Although we have, as yet, no information on the point, it seems to us not unlikely that the human infant could also have similar reactions. In this event, the implications in pædiatrics are self-evident, and we would be extremely interested to hear of relevant clinical evidence.

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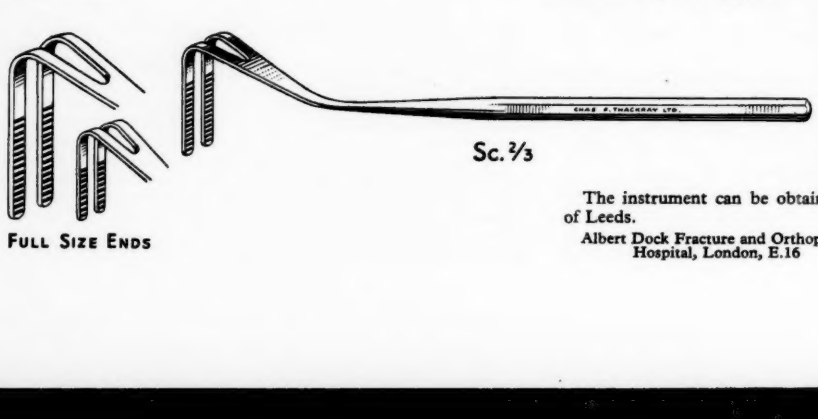
New Inventions

NEW RETRACTOR FOR HAND SURGERY

SATISFACTORY retraction in hand surgery is sometimes difficult to obtain, particularly as the standard retractors are far too large.



Sc. 2/3

FULL SIZE ENDS

The retractor shown in the accompanying figure has been found very useful in cases, such as Dupuytren's contracture, where dissection is being carried out by undercutting. The instrument is 5 1/2 in. long, and the blades are 1 in. long. A smaller model with 1/2-in. blades is also obtainable. The part of the handle nearest the blades is angled backwards, so that the line of pull is opposite the centre of the blades. The blades are at right-angles to the line of pull; their upper surface is notched to prevent slipping. Gentle retraction is possible, with a direct pull at right-angles to the skin surfaces; this does not roll up the skin edges, and does not greatly obstruct the view.

The instrument can be obtained from Chas. F. Thackray Ltd., of Leeds.

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Reviews of Books

Biochemical Aspects of Neurological Disorders

Editors: J. N. CUMINGS, M.D., F.R.C.P., professor of chemical pathology, Institute of Neurology, London; MICHAEL KREMER, M.D., B.SC., F.R.C.P., consultant neurologist, National Hospital, London. Oxford: Blackwell Scientific Publications. 1960. Pp. 230. 37*s*. 6*d*.

THIS timely and useful production outlines the biochemical background and the clinical picture in a number of neurological diseases at present thought to be due primarily to biochemical lesions. The exposition of the purely biochemical aspects is particularly useful since it allows the general principles to be considered and invites their application to disease processes of still unsettled ætiology. The book is of a generally high standard and the presentation is admirably clear.

Sir Charles Symonds has been a pioneer among clinicians in emphasising the importance of the biochemical lesion in neurology. Appropriately, therefore, he contributes a thoughtful and thought-provoking review of demyelinating diseases, in which he draws together the established clinical and pathological facts which must be accounted for in any explanation of biochemical mechanisms. Among much that is excellent, Dr. W. W. Payne's discussion of calcium and phosphorus metabolism and Prof. N. F. Maclagan's consideration of the biochemistry of coma are particularly interesting. The chapter on the biochemistry of muscle disorders by Dr. Brian McArdle is valuable both for the review of what is known and for the clear exposition of unsolved problems. Dr. J. St. C. Elkington's succinct account of the clinical aspects of porphyria emphasises the value of symptomatic treatment where natural remission from an attack is so likely.

This book will appeal widely to clinicians, and it may surprise some to find that such a variety of biochemical lesions are already clearly recognised in neurology: for others the detailed outline of the chemistry involved will add to their understanding and handling of the clinical condition.

A Guide to the Identification of the Genera of Bacteria

V. B. D. SKERMAN, B.AGR.SCI., reader in bacteriology and head of the department of bacteriology, University of Queensland. Baltimore: Williams & Wilkins. London: Baillière, Tindall, & Cox. 1959. Pp. 257. 44*s*.

BACTERIOLOGISTS sometimes have difficulty in naming unfamiliar organisms which they isolate. This applies seldom to the well-known pathogens of man, animals, and plants, which are easy to recognise, but to commensal or saprophytic organisms which sometimes colonise or merely contaminate pathological lesions or may be found in natural materials examined in the laboratory. Matching the identifying characters of unknown with known isolates by hunting through the pages of *Bergey's Manual* or a major textbook is not perhaps the most orderly or satisfying way of meeting this difficulty, although it is certainly the commonest. To help bacteriologists with this problem Mr. Skerman has devoted much patient labour to preparing a comprehensive key to the genera of bacteria. After having determined the characters of the unknown organism, the bacteriologist begins at the beginning of the 48-page key, and reads through it until he reaches the point at which he can identify his organism. As he reads, he answers a series of questions which the key puts to him in a defined order. As each question is answered, the key supplies the number of the next section to be consulted until finally a generic name is given along with the next number to be consulted. Thus, the key puts the bacteriologist more quickly than he could otherwise expect in touch with the genus in which he will finally identify the species of his troublesome organism. From that point the key is used along with standard texts or manuals assisted by the Guide's own digest of genera (largely, by agreement, from *Bergey's Manual*) and by use of its own methods for carrying out tests of value in identification.

This interesting volume will have to be tested by use before its value may be finally assessed. Meanwhile it may be welcomed for what it seeks to do, even if its place in medical laboratories may not be so readily assured as in laboratories devoted to other parts of bacteriology.

Diagnosis in Locomotor Disorders

KENNETH STONE, D.M., M.R.C.P., physician, Arthur Stanley Institute for Rheumatic Diseases, The Middlesex Hospital. London: Oxford University Press. 1960. Pp. 224. 25*s*.

THE art of differential diagnosis scorns the artificial frontiers drawn round the specialties of medicine, and the merit of a book which deals with it can be measured by the freedom with which its author roams across these boundaries. By this standard Dr. Stone has done well: he has applied himself not only to conditions which produce pain, deformity, inflammation, or defective function in the locomotor system but also to peripheral vascular diseases, involuntary movements, and paræsthesiæ. The book is arranged in part on a regional basis, dealing with the differential diagnosis of pain in specific joints or areas, partly in sections devoted to individual signs or symptoms. The reader is guided past the pitfalls which await the unwary—the patient whose " rheumatism " is really metabolic bone disease, the arthropathy which is not rheumatoid arthritis but indicates a bronchial carcinoma. Many readers will be grateful for help, which standard textbooks often fail to give, on subjects such as acroparæsthesiæ. The book is liberally illustrated with radiographs; these have been well chosen, but the reproduction (positive in some, negative in others) is not always adequate. An appendix gives the normal values for a selection of laboratory tests.

In a book modest in size and price Dr. Stone has provided a useful and practical guide which general practitioners and specialists of many kinds will welcome.

The Cell of Schwann

GILBERT CAUSEY, M.B., F.R.C.S., professor of anatomy, Royal College of Surgeons of England. Edinburgh: E. & S. Livingstone. 1960. Pp. 120. 21*s*.

THIS small book has a somewhat deceptive title which suggests at first glance that its scope is very restricted. In fact a great deal of ground is covered and much interesting and up-to-date information is recorded about the structure of peripheral nerves, their degeneration and regeneration, and even their tumours. The author has himself done much research work on nerves, using laboratory animals and studying nerves not only with the light microscope but with the electron microscope. The pictures and diagrams are easy to decipher, even by one not expert in electron microscopy. The brief historical section is pleasantly informative. Among the spate of short monographs which are pouring out at present this one is well worth reading by all those interested in the nervous system.

Auscultation of the Heart

ABE RAVIN, M.D., associate clinical professor of medicine, University of Colorado School of Medicine. Chicago: Year Book Publishers. London: Interscience. 1959. Pp. 166. 45*s*.

A SHORT volume on clinical auscultation of the heart is welcome, and this is in fact probably the best of the few short monographs on this subject.

The general principles of sound and of phonocardiography are briefly discussed and adequate phonocardiograms are used to illustrate the text, although the author sensibly makes it clear that a phonocardiogram is only as good as the person who takes it. The book is to be strongly recommended for its subject matter and its clear presentation, and it is well written. Close reading, however, reveals some occasional surprising statements, which are more conspicuous because of the generally high level of the text. Despite modern views to the contrary, it is stated that the heart is always enlarged in acute rheumatic carditis and that this is responsible for the mid-diastolic rumble. The timing and pattern of systolic murmurs do not seem to receive sufficient emphasis. The murmur of ventricular septal defect is described as diamond-shaped while

it is in fact pansystolic, and no mention is therefore made of this useful method of distinguishing a ventricular septal defect from a short-ejection innocent systolic murmur. The section on gallop rhythm is confusing, mainly because of the perpetuation of the term "protodiastolic" (protodiastole begins in systole) for the third heart-sound, which is thought not to be physiological on other grounds. There is confusion between atrial and third sounds, for gallop rhythm is said to be rare in atrial fibrillation. It should be clearly stated somewhere that an atrial sound, though abnormal, is not evidence of failure, while the third sound in older subjects is good evidence of raised atrial pressure.

A Short Synopsis of Human Protozoology and Helminthology

L. R. S. MACFARLANE, O.B.E., M.D., D.P.H., professor of pathology, Royal Army Medical College, London. Edinburgh: E. & S. Livingstone. 1960. Pp. 251. 35*s*.

THIS book is based upon the class-notes issued in the author's department at the Royal Army Medical College. It is mainly an epitome of Craig and Faust (and there could be no better source of accurate information), which means that the emphasis is zoological rather than pathological. As a companion to lectures and laboratory classes it will help many students to identify and describe accurately the commoner protozoa and worms parasitic on man, but those who want to know more than a smattering about the reactions of the body to infestation or the related problems of epidemiology must seek elsewhere. The illustrations (by R. M. Leach) are good. Colour photography may ultimately surpass the best water-colour, but it has not done so yet. It is a pity that the small size of the book makes it necessary to print the captions on the reverse of some of the plates. The line drawings would be improved if there was some indication of their scale. Some emphasis is placed upon the differences in pigment produced by the species of plasmodium, but it is not clear from the text where this pigment may be seen. Hydatid disease occurs in many other places than those listed. There is no evidence that trichomonal vaginitis can be cured by changing the pH of the vagina (already often as low as 5·2) and antibacterial measures. The symptoms attributed to whipworms seem exaggerated in the light of common experience. Threadworm, the common English name for *Enterobius vermicularis*, does not appear in the index. The technical appendix is clear, but if this book is used outside the classroom (as it certainly will be) the procedures mentioned in the text (e.g., concentration methods for fæces) should be included. The printing is not really a success: because only one size of capitals has been used (and that rather too large for the page) and because italics are used without any consistent rule, it is hard to find one's way in the text and the book is tiring to read.

On the Threshold of Delinquency

JOHN BARREN MAYS, M.A. Liverpool: Liverpool University Press. 1959. Pp. 243. 25*s*.

THIS book is essentially the story of an evening club for selected boys, age 8 to 13, living in a slum district of a seaport city, seemingly Liverpool, the club deliberately planned to have a majority membership of actual or likely lawbreakers. The book describes and analyses the venture's first four "experimental" years, with detailed accounts of many of its members and their response—or lack of response—to its attempts to help them by collective and individual means ("groupwork" and "casework"). The club was designed to attempt a rough estimate of the parts played by personal emotional disturbance and by domestic and local environment, including locally accepted values and behaviour, in the making of young delinquents, and with the confessed hope that the latter influences might be found to predominate in many cases and might respond to treatment less recondite, individual, and costly than that of the psychiatrist and child-guidance clinic.

It may seem surprising that any inquiry should be necessary to show that environmental influences so obviously powerful as those described in a chapter on "the subcultural background" are in fact powerful; but if it was needed, here it is. Here also is evidence that if and when all the people in authority, notably parents, can be induced to work together for good, then good may be expected, and that to induce them so to work is extremely difficult. The book should interest both social workers and those able to influence or alter the environment in which thousands of our fellow citizens are born and grow to maturity.

The Care of the Aged in Norway

FINN DANIELSEN. Oslo: Norwegian Joint Committee on International Social Policy. London: Bailey Bros. & Swinfen. 1959. Pp. 56. 6*s*.

IN common with the rest of Western Europe the Norwegians face the problem of a rapid increase in the numbers of old people, both absolutely and in proportion to the population as a whole. Their solutions are broadly similar to our own, though the distinction between hospitals and welfare hostels is not apparently as clear as it is in this country. The Norwegians believe in helping old people to live in their own homes as long as possible, but it sounds as if their system of home-helps is less highly developed than our own. Special importance is attached to old people's housing.

The Scandinavian countries have a reputation for treating their old people generously in the matter of pensions, but it is hard to compare the schemes described in this book with the systems of old-age pensions supplemented by National Assistance used in this country.

The book is ably written and profusely illustrated. The pictures probably show the best rather than the typical, but they suggest that before long Norway will be second to none in her arrangements for the care of the aged.

Significant Trends in Medical Research (*Ciba Foundation Tenth Anniversary Symposium*. London: J. & A. Churchill. 1959. Pp. 356. 50*s*.).—The Ciba Foundation celebrated its tenth anniversary by a special colloquium which must have been a stimulating experience for those privileged to attend, and, edited by Dr. G. E. W. Wolstenholme, Miss Celia M. O'Connor, and Miss Maeve O'Connor, makes fascinating reading. The speakers were distinguished specialists, some of them Nobel prize-winners, and the subjects discussed ranged from molecular structure to kwashiorkor. There were papers on the pyridine nucleotide enzyme complexes, virus multiplication, population dynamics of body cells, genetics, neurophysiology, the mechanism of action of hormones, insulin, pulmonary disease, malignant transformation, hypertension, and medical research in the United States. The speakers were asked to pick out those developments in their special fields in the past few years which they thought would prove to be the most significant in the next. This good idea gave rise to some very interesting thoughts and discussion, for the future was in the minds of the participants all the time.

There are some generalisations here and there, and strivings after generalisations, which should inspire teachers and investigators and direct them in the way they ought to go. This is a book to keep, for it will be splendid reading for years, and it will have a historical value for all time.

Proceedings of the First International Congress of Neurological Sciences (*Vol. III. Electroencephalography, Clinical Neurophysiology, and Epilepsy*. London and New York: Pergamon Press. 1959. Pp. 707. £7.).—The First International Congress of Neurological Sciences was held in Brussels in July, 1957. Though it must have been one of the largest specialist congresses ever held, this did not daunt the secretary-general, Dr. Ludo van Bogaert, and Dr. J. Radermecker from tackling the formidable task of editing the proceedings. This is the first of five volumes to appear and contains 135 papers. The text is 'Varityped', with abundant recordings, charts, and some plates.

Laboratory Manual of Pediatric Micro-Biochemical Techniques.—In our review of May 7 we stated incorrectly that this book is published in London by H. K. Lewis. The University of Colorado Medical Press are the sole publishers.

THE LANCET

LONDON 11 JUNE 1960

Too Many Calories

WHILE a large section of the world's population subsists on an inadequate diet, in other communities excessive intake of calories gives rise to serious medical and social problems. The Food and Agriculture Organisation of the United Nations has been created to deal with international undernutrition: the pharmaceutical industry continues to seek means of saving the victims of their own appetites from the consequences of overeating, and surgeons are devising operations for the removal of unwanted fat.[1]

In a recent symposium at the Mayo Clinic, GASTINEAU [2] concluded that " no definite metabolic abnormality has been demonstrated as a cause for human obesity ". This cannot be denied; but recent developments—for example, the work of CHALMERS and his colleagues at the Middlesex Hospital—have brought a little light. In 1958 these workers [3] reported the presence of fat-mobilising activity in the urine of healthy people who had been fasting, and that this activity could not be detected when obese subjects were given 1000-calorie diets containing 90% carbohydrate, whereas it was enhanced when the diet contained 90% fat. A further report [4] from the same department describes the purification and properties of the material responsible for these effects. Subcutaneous injection into mice of urinary extracts from subjects on a restricted carbohydrate intake or fasting was followed by a fall of blood-sugar, while the blood lipids and ketones, as well as the liver-fat concentration, increased. When a series of injections was given, the animals lost weight without their appetites being affected, and the loss of weight was found to be due to reduction in the body fat and water content, the protein content apparently remaining unchanged. Since this activity could not be detected in the urine of patients whose pituitaries had been damaged or removed, the Middlesex group suggest that the material responsible is of pituitary origin. They remark that, of the hormones known to be produced by the pituitary, the material in the urine extracts most closely resembles corticotrophin.

Meanwhile the problem of managing the overweight patient remains, and the plethora of advice is some measure of the failure of any simple method of management to produce consistently successful results. Two double-blind trials in Edinburgh on the comparative value of phenmetrazine hydrochloride and other drugs in the management of obesity are reported in this issue. Dr. DUNCAN and his colleagues (p. 1262) studied " refractory " obesity in a group of patients, diabetic and non-diabetic, who had been under observation for at least a year, and who despite dietetic advice had failed to lose weight in the three months preceding their admission to the trial. Two drugs were tested: in contrast to the findings of YUDKIN,[5] methyl cellulose was found to be without effect; but phenmetrazine, administered for eight weeks in the doses usually recommended, was associated with a greater rate of weight loss than that in periods in which dummy tablets were given. Dr. HAMPSON and his colleagues (p. 1265) compared the value of phenmetrazine, dexamphetamine, and control tablets in the same patients, and concluded that both the drugs had some value in accelerating loss of weight. They noted, however, that the rate of weight loss diminished as the trial continued, whether the drugs or the control tablets were being used.

The controversy created by BANTING in 1863 [6] has been renewed from time to time—most recently by KEKWICK and PAWAN.[7] They showed that obese patients lost more weight when consuming diets containing 90% fat than when the diets were predominantly of protein or carbohydrate. The periods of study were short, amounting to less than ten days in each patient. Two further investigations on similar lines indicate that the usual rapid fall in weight when a diet with a high fat content is consumed is due to changes in body-water content rather than to any change in calorie requirements or expenditure. OLESEN and QUAADE [8] studied eight obese women who remained on a high fat and low carbohydrate intake for periods of nine to twenty-two days, with an initial control period on an unrestricted diet, and a later period on a diet with a high carbohydrate content. On the high-fat regimen considerable initial loss of weight was soon followed by restoration of equilibrium, and weight continued to be lost at a rate in keeping with the calorie content of the diet, whatever its chemical nature. PILKINGTON and his colleagues [9] studied the losses of weight of nine very obese patients who were maintained on constant diets providing 800–1000 calories daily, predominantly either fat or carbohydrate. They showed convincingly that when the diet is changed from a high fat to a high carbohydrate content, with the total calorie intake kept constant, then weight is gained. Change to a high fat intake led to relatively sudden loss of weight: in ten days patients might lose as much as 2·5 kg. in excess of the anticipated loss, but thereafter their loss of weight continued at the same steady rate whether their diet was provided mainly from fat or from carbohydrate. These sudden gains and losses of weight with changes in diet they attributed to changes in fluid balance.

Some evidence on this point has been published by FURNASS,[10] who measured oxygen consumption and carbon-dioxide excretion continuously for periods as

1. Clarkson, P. *Brit. med. J.* 1959, ii, 1334.
2. Gastineau, C. F. *Proc. Mayo Clin.* 1960, **35**, 119.
3. Chalmers, T. M., Kekwick, A., Pawan, G. L. S., Smith, I. *Lancet*, 1958, i, 866.
4. Chalmers, T. M., Pawan, G. L. S., Kekwick, A. *J. Endocrin.* 1960, **20**, 21P.
5. Yudkin, J. *Lancet*, 1959, ii, 1135.
6. See *ibid*, 1958, ii, 785.
7. Kekwick, A., Pawan, G. L. S. *ibid*. 1956, ii, 155.
8. Olesen, E. S., Quaade, F. *ibid*. May 14, 1960, p. 1048.
9. Pilkington, T. R. E., Gainsborough, H., Rosenoer, V. M., Carey, M. *ibid*. April 16, 1960, p. 856.
10. Furnass, B. *J. Physiol.* 1959, **150**, 11P.

long as twenty-four hours. He studied subjects previously "saturated" with carbohydrate, and compared the effects of giving 1000 calories as dextrose or as cream. When the cream was given the respiratory quotient (R.Q.), as expected, was 0·7; but, on the other hand, when the dextrose was given the R.Q. did not rise to unity, as might have been foretold on the basis of complete combustion of the carbohydrate. FURNASS continues:

> "when computations were made in terms of element balance, it appears that up to 50 g. per day of oxygen consumed may not have been used for combustion in the accepted sense of the word. These observations are compatible with the hypothesis that unexpectedly low respiratory quotients may represent the combinations of some absorbed oxygen with hydrogen atoms in depot fat, thereby resulting in desaturation of the fat with change in its physical properties. . . . It is suggested that such a mechanism could reflect a process of adaptation to the external environment, a possibility that cannot be detected by applying the commonly accepted concepts of indirect calorimetry."

This important work may provide a key to some of the problems raised by the studies with high fat and high carbohydrate diets to which we have referred.

Appetite is particularly difficult to study in man; but perhaps some of the successes claimed in the past for various types of diet have been due to their effect on appetite, or even perhaps on activity—a factor commonly ignored. Certainly there is still no reliable evidence that changes in diet of the type described alter the efficiency with which the body derives its energy from the food consumed. If appetite can be controlled by a high fat diet or some other modification with a high satiety value, this might be more effective than attempting to persuade the obese to practise dietary continence. As regards appetite-controlling drugs, the two articles we publish today confirm that phenmetrazine and dexamphetamine have some limited value. But with both drugs there is danger of addiction [11]; and phenmetrazine has now been added to the list of Schedule IV substances so that it can no longer be obtained without a prescription. There is still an unfilled need for a drug which is consistently reliable, safe, and cheap.

Surgical Treatment of Pancreatitis

THE pancreas, lying securely ensconced on the back wall of the abdomen, offers a therapeutic challenge to surgeons which is now being taken up.

Pancreatitis is perhaps best considered under the headings "acute" and "chronic relapsing"—though, as SINCLAIR [12] has pointed out, "acute pancreatitis" covers a wide range of conditions, from the most fulminant of abdominal emergencies to subclinical disturbances detectable only by biochemical measurements. Clinically acute pancreatitis simulates visceral perforation very closely.[13] In pancreatitis the pain may be more agonising, but the abdominal rigidity is not so general or so constant. Cyanosis and slight jaundice are commoner in pancreatitis; it usually occurs in fat subjects, and there is a definite alcoholic history in a fairly high proportion of cases—up to 25% in American series.[12] The discoloration of the flanks (Grey-Turner's sign) and discoloration at the umbilicus (Cullen's sign) do not become evident early enough in the disease to be of practical value in distinguishing between acute pancreatitis and a perforated peptic ulcer for the purpose of managing acute pancreatitis without operation.[14] The serum-amylase level is raised initially, and gross elevation is almost pathognomonic; but in perforation of a peptic ulcer and in other abdominal conditions the serum-amylase may be raised to comparable levels.[12] Urinary diastase is usually increased, and glycosuria may be found; diabetes may result.[14] In the important new field of X-ray investigation of the acute abdomen by means of oral contrast media, SAMUEL [15] has described widening of the C curve of the duodenum, forward displacement of the stomach, and changes in the duodenojejunal flexure produced by the acutely inflamed pancreas.

In the treatment of acute pancreatitis, operation is usually avoided in the first instance unless it is needed to establish the diagnosis. Where the diagnosis is in doubt, laparotomy is best undertaken; and it probably does not increase the mortality in the early stage. If the abdomen has been opened and acute pancreatitis found, the biliary system may usefully be decompressed; for, whatever pressure differential may have existed between the pancreatic and biliary ducts before treatment is begun, the deliberate inhibition of pancreatic secretion, which is part of the therapeutic programme, will reduce pressure in the pancreatic ducts below that in the biliary tree and so favour the reflux of bile. ELLIOTT et al.[16] have emphasised the importance of emptying the biliary tree of any mixture of bile and pancreatic juice—a mixture which they have shown to be particularly virulent—and choledochostomy or cholecystostomy is therefore a sound procedure. This procedure is also anatomically sound: almost always in acute pancreatitis the pancreatic and bile ducts are found to have a common opening in the duodenum—this arrangement was found in 20 of 21 fatal cases in SINCLAIR'S [12] series.

Whether the abdomen has been opened or not, restoration of blood-volume is essential; much fluid can be lost from the circulation by the widespread retroperitoneal inflammatory exudation.[17] Some clinicians advocate the use of cortisone or corticotrophin for its effects on the shock and its anti-inflammatory effects. For reduction of the secretory activity of the pancreas continuous gastric aspiration should be applied, in order to remove gastric hydrochloric acid, which, through the secretin mechanism, has a powerful stimulant effect on the pancreas. Drugs which actually inhibit pancreatic secretion, such as atropine or propantheline, should be administered; there is some experimental

11. See *Times*, Jan. 19, 1960.
12. Sinclair, I. S. R. *J.R. Coll. Surg. Edinb.* 1959, **5**, 57.
13. Cope, Z. The Early Diagnosis of the Acute Abdomen. London, 1946.
14. Cattell, R. B., Warren, K. W. Surgery of the Pancreas. Philadelphia, 1953.
15. Samuel, E. *Brit. J. Radiol.* 1960, **33**, 82.
16. Elliott, D. W., Williams, R. D., Zollinger, R. M. *Ann. Surg.* 1957, **146**, 669.
17. Keith, L. M., Jr., Watman, R. N. *Surg. Forum*, 1955, **5**, 380.

evidence that hexamethonium is slightly more effective,[18] and propylthiouracil has also been used.[19] For the relief of pain pethidine is preferable to morphine because it causes less contraction of the duodenum. If the patient is not shocked, nitrites help by relieving spasm of the sphincter of Oddi. Epidural and splanchnic block have been advocated for relief of severe pain, and have been claimed to have a beneficial effect on the cause of the disease by improving the blood-supply to the pancreas.[20]

Acute pancreatitis, including the rare postoperative variety, is a highly lethal condition. If the patient survives the early phase he may die later when the pancreas has become simply a mass of infected slough. In cases, therefore, which are hanging fire or deteriorating with recurrent pyrexia, surgical drainage of the peripancreatic tissues (which has nothing to offer in the early stages) and excision of sloughs may be life-saving. The administration of antibiotics to control secondary infection is important throughout the treatment of acute pancreatitis; and one of the tetracyclines is generally employed for this purpose.

The management of the patient with relapsing pancreatitis is controversial and will probably remain so until the underlying causes are better understood.[21] Many different procedures have been advocated; and a balanced view has been given by RODNEY SMITH.[22] In chronic relapsing pancreatitis the pancreas is especially vulnerable; and if, anatomically, biliary reflux is possible and likely to precipitate further acute episodes it is rational to divert the bile from the pancreatic duct. This can be done by sphincterotomy, in which the "common channel" is laid open so that the common bileduct and pancreatic duct open independently into the duodenum. The operation is best done under direct vision after anterior duodenotomy.[22] The length of the incision dividing the sphincter is usually 4–5 mm. BARTLETT and NARDI [21] recommend more extensive division of the posterior duodenal wall and the anterior wall of the common duct proximally for 1·5 cm., dividing not only the common sphincter of both ducts at the end of the papilla but also the muscular sling within the duodenal wall, described by BOYDEN,[23] which also surrounds both ducts. Sphincteroplasty with mucosal suture, by various methods and sometimes with a wedge resection of the sphincter, is preferred by some surgeons.[24] Sphincterotomy, laying open the common channel, exposes the duct of Wirsung, which can then be catheterised and operative pancreatograms obtained.[22] BARTLETT and NARDI [21] have carried out sphincterotomy and transduodenal exploration of the pancreatic duct in 53 cases, recently adding pancreatography as a standard part of the procedure. In these operations anatomical variations in the definition of the ducts must be remembered; the accessory duct of Santorini may be the main pancreatic duct, and if stenosed may have to be enlarged.[21]

Distal pancreatectomy and retrograde ductal drainage, by removal of the pancreas distal to the neck together with the spleen, clearance of stones from the duct system in the remaining head, and anastomosis of the divided duct to a jejunal Roux loup, secures retrograde drainage. AIRD and BUCKWALTER [25] have described the operation of removing the left part of the gland and implanting the cut end into a Roux loop of jejunum. AIRD emphasises the title "retrograde pancreaticojejunostomy" for this operation rather than "caudal pancreaticojejunostomy"; for, as ROSS [26] showed, the tail of the pancreas is a very short and somewhat variable structure. In many cases, however, the head of the gland is the main site of the disease; drainage of the main duct, leaving the choked smaller ducts and acini, proves inadequate, and pancreatoduodenectomy must be considered—though, unless there is a definite suspicion of malignancy, most surgeons would think twice before embarking on this formidable procedure.

Pancreatojejunostomy—anastomosis in continuity of the duct of Wirsung to a jejunal loop—has been recommended by some.[14 27] Pancreatic denervation, though without effect on the pancreatitis itself, is worth considering in view of its effect in relieving pain; direct nerve section of the branches coming from the right and left cœliac ganglia to the head of the pancreas can be carried out. In certain cases, when a firm thickening is encountered in the pancreas, associated with jaundice, the older operation of cholecystenterostomy, by relieving tension in the biliary tract, may prove worth while.[28]

18. Palmer, J. D. *ibid.* 1952, **1**, 560.
19. Reid, L. C., Paulette, R. E., Challis, T. W., Hinton, J. W. *Surgery*, 1958, **43**, 538.
20. Marion, P. *Lyon chir.* 1945, **40**, 315.
21. Bartlett, M. K., Nardi, G. L. *New Engl. J. Med.* 1960, **262**, 643.
22. Smith, Rodney, *in* Recent Advances in Surgery (edited by S. Taylor). London, 1959.
23. Boyden, E. A. *Surg. Gynec. Obstet.* 1959, **104**, 641.
24. Jones, S. A., Smith, L. L., Gregory, G. *Ann. Surg.* 1958, **147**, 180.
25. Aird, I., Buckwalter, J. See I. Aird, *Lancet*, 1957, i, 1199.
26. Ross, J. A. *ibid.* 1957, ii, 45.
27. Duval, M. K., Jr. *Surgery*, 1957, **41**, 1019.
28. Edwards, H. C. *in* Recent Advances in Surgery. London, 1954.
29. Memorandum H.M.(60)28.

Annotations

SHORTAGE OF RADIOGRAPHERS

THE shortage of radiographers in the National Health Service has been causing much anxiety for several years. Admittedly recruitment has improved somewhat, but wastage is very great. A large majority of new students are women, of whom some never qualify and many leave soon after qualification to marry or to do other work. It is estimated that a third of all qualified women radiographers leave within a few years of completing their training and only a few ever return. There is now a shortage in establishment in England and Wales of about 500 radiographers, and this is seriously impairing the efficiency of hospital radiological departments. The Ministry of Health appointed a study group to investigate the shortage and to determine its causes. The report of the group has now been received and certain suggestions [29] have been put by the Minister of Health to hospital authorities.

The shortage is unevenly distributed and is greatest in remote and unattractive districts. In some areas the main cause is still the lack of training facilities, and regional boards are advised to review their training arrangements, in consultation with the teaching hospitals, to see whether additional schools can be provided. But staffing is

unsatisfactory even in many areas with excellent training schools, and all regions are more or less understaffed. The position tends to be worst in prosperous industrial areas of the North and Midlands where there are many attractive openings for young people and strong competition from industry for male and female labour.

The study group found that vigorous local publicity to attract students was often successful, and they recommend advertisements in local papers, talks by the radiologist or the superintendent teacher of radiography to upper forms of local schools, and the holding of "open days" at local hospitals at which schoolchildren could see at first hand the work of the radiographer and the X-ray department. The Minister hopes that by wider publicity and by the extension of training facilities the recent improvement in recruitment will be carried further, and that more men will enter the service (this is vital if the more senior posts are to be staffed and maintained).

The Ministry memorandum refers to apprehension among students and their parents about possible dangers of radiation. Good publicity methods could counteract the sensational statements that appear from time to time and explain the very strict regulations now in force for the protection of staff and patients. Unsatisfactory working conditions and staff relationships and inadequate amenities are sometimes contributing to staffing difficulties, and hospital authorities are urged to do everything possible to improve conditions. A constant source of dissatisfaction among radiographers is the increased pressure of work, aggravated by staff shortages and the stress of emergency calls. The Minister suggests that hospital medical committees draw up criteria to assist junior medical staff in deciding when to call for an "emergency" X-ray examination, bearing in mind the general recommendations in part III of the interim report of the Adrian Committee on radiological hazards, concerning technical aspects and administrative arrangements to minimise the number of X-ray examinations. The Minister also hopes that hospital authorities will do everything possible to encourage married women to return to the service, either part-time or full-time, when their family commitments allow. An increase in the maximum rates of grant for student radiographers has been announced by the Ministry.

Salary scales and promotion prospects are not mentioned in the memorandum, though these are the most important means of stimulating recruitment and maintaining adequate staffs. After long negotiations and arbitration new scales were agreed in August, 1959, which are a considerable improvement. The starting salary of £500 is attractive to a young woman on qualifying but less so to a family man with many other opportunities in industry. The maximum points in all grades are too low and there is often little or no prospect of promotion for many years. An increase in the establishment of senior-radiographer posts would provide more incentive, and more appointments as superintendent radiographer (grade 1) would encourage young men to remain in the service. Even in the superintendent-radiographer grades the maximum salaries are still too low and compare unfavourably with those in the administrative grades of the National Health Service of comparable seniority and responsibility, and a recent arbitration award for administrative and clerical staff has further increased the differentials. Substantial increases are required in the higher grades if the quality of the service is to be maintained and improved and if men of ability and initiative are to remain in the X-ray departments and become teachers in training schools. In this respect regional hospital boards might be given more discretion to provide larger additional allowances for special qualifications or responsibility, particularly in large training schools.

The Faculty of Radiologists also considered in detail the causes and consequences of the shortage, in their memorandum of December, 1959. They drew attention to the very grave situation in many departments where there is serious overwork, inadequate supervision of junior staff, and an inevitable lowering of standards. The difficulty of obtaining locums during holidays and sickness has been so great in some places that the services of private X-ray firms have had to be called upon. The faculty emphasised that radiographers are carrying out important, skilled, and responsible work and their status and conditions of work require special consideration. Among other constructive proposals are suggestions for revising and simplifying the syllabus and stimulating clinical interest; more generous training grants; and a special living allowance in addition to a training grant for students wishing to train and then work in an isolated district. Some form of additional incentive payments might well encourage qualified radiographers to take up posts where the need is greatest. Another suggestion is that students should be accepted at 17, and some training schools already have junior assistant posts in which girls leaving school are given paid work in the X-ray department until they are old enough to begin the course.

Drastic and vigorous action is necessary if the crisis is to be resolved, and it may well be that a combination of these proposals will be necessary for success.

TREATMENT OF DIABETES INSIPIDUS

CHLOROTHIAZIDE and certain of its analogues have proved effective in the treatment of diabetes insipidus. Crawford et al.[1] administered chlorothiazide 1 g. or hydrochlorothiazide 0·1 g. (doses for adults) daily by mouth in three or four divided doses to seven patients with this condition, and showed that these drugs increased urinary solute and decreased urinary flow. Within two hours of ingestion of the drugs excretion of sodium increased abruptly, and later that of potassium. Excretion of chloride increased and urinary pH rose. Although an increase of urinary flow was not a regular finding, in the first six hours excretion of water usually exceeded fluid intake, and up to about 1 kg. body-weight was lost in the first twenty-four hours. The excretion of sodium began to decline within eight hours after treatment was started, and of potassium within fifteen hours. Potassium deficiency invariably developed but was readily overcome by giving potassium chloride orally in a dosage of 3 g. daily throughout the period of treatment. Eventually an electrolyte-water equilibrium was established and the weight returned to the initial level.

The action of chlorothiazide in diabetes insipidus seems to be specific. It was compared with that of acetazolamide, dichlorphenamide, and mersalyl; but none of these increased osmolar clearance without increasing water clearance proportionally. The action of chlorothiazide on osmolarity was independent of water clearance, and patients and healthy control subjects to whom chlorothiazide was administered still responded to a water-load with rapid diuresis. Chlorothiazide, moreover, acted independently of vasopressin but enhanced its effect. It was also effective when resistance had developed to vasopressin, and in patients with diabetes insipidus of nephrogenic origin where there was no deficiency of vasopressin.

1. Crawford, J. D., Kennedy, G. C., Hill, L. E. *New Engl. J. Med.* 1960, **262**, 737.

The chlorothiazide group of drugs are unlikely to find an important place in the treatment of patients with diabetes insipidus who are satisfactorily controlled with vasopressin. Besides causing depletion of potassium this group is said occasionally to cause thrombocytopenia and agranulocytosis, and possibly jaundice. These drugs may, however, find a useful place in the treatment of diabetes insipidus of nephrogenic origin, and perhaps also in cases of vasopressin deficiency which have become resistant to hormone treatment.

IN LODGINGS OR IN RESIDENCE?

As Prof. Melville Arnott has pointed out,[1] the great merit of Oxford and Cambridge lies in their collegiate life: "the members of these societies go out each day to their classrooms, laboratories, and libraries but return each night to eat together, to meet their tutors, to read, and above all to talk together in hall, in common-room, and in each others' rooms." Remarking that "British universities in general are very far from providing these priceless opportunities", Professor Arnott said that in his own university of Birmingham only 12% of the full-time students were in residence; of the present total of nearly 4100, 24% live at home and 64% in lodgings. All who recognise the value of the contribution that Birmingham is making and can make will be glad to hear of the appeal now launched to provide places for 1480 students and staff. Given a full response, the hope is that by 1965 a third of the 5500 students will be in residence.

Dr. Robert Aitken, the vice-chancellor, recalls that the newer universities of the great industrial cities were at first purely civic universities, attended by students who lived in their own homes. But Birmingham is now, of course, a national university as well: over half its students come from other parts of the country, and over 10% of them from overseas. The community at large looks to its universities for graduates showing breadth of education, knowledge of men, and ambition of a worthy kind:

> "Our aim", says the appeal, "is to produce men and women who are intellectually honest, unselfish in their behaviour, sensitive, competent at the tasks for which they train themselves, and genuinely interested in their fellows. For this we rely traditionally, not on measures of control and indoctrination, but on the free play of human contacts and shared enterprise among the students themselves and among students and staff. The great opportunities for these are in the Union, in the places where games are played, and—most important of all—in the communal life of halls of residence."

Five years ago Birmingham University bought 45 acres of open parkland within ten minutes' walk of its main Edgbaston buildings. On the design of Sir Hugh Casson and Neville Conder, seven new halls are to be built on that site—some high, some low, and mostly grouped in pairs so that they can share diningrooms, kitchens, and other service buildings. The estimated cost of this attractive and imaginative plan is £2,588,250, of which the University Grants Committee have agreed to provide £500,000 and £1,638,250 has still to be found. Contributions or inquiries should be addressed to the secretary of the University, Edgbaston, Birmingham 15.

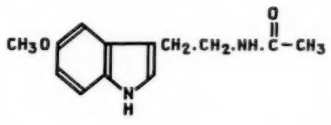
Professor Arnott, perhaps too hopefully, said that to make all the universities of Great Britain completely residential would cost £90 million. It would be money well spent.

1. Arnott, W. M. *Lancet*, 1959, i, 1.

MELATONIN

IF the Cartesian concept of the pineal gland as the seat of the soul is no longer tenable, it has been singularly difficult to replace. Lerner and his colleagues [1] have isolated from bovine pineal a principle which lightens frog skin and has the power to block and reverse the darkening action of pituitary melanocyte-stimulating hormone. This substance, which they have called melatonin, is the most potent lightening agent known—about 10^5 times more effective than noradrenaline and acetylcholine, which previously were the most potent of these agents that had been recognised.[2] To a lesser extent such diverse compounds as 5-hydroxytryptamine, cortisol, triiodothyronine, and acetazolamide have this action, which results from the aggregation of melanin-containing granules around the nucleus of the intact melanocyte.[3] Aggregation is associated with a change in the colloidal state of the cytoplasm of the cell from sol to gel, with a consequent indirect inhibitory effect on melanin formation. Thus, melatonin injection will cause decreased production of melanin in hamster melanoma.[2]

The pineal gland contains minute amounts of melatonin. Many kilogrammes of tissue were used during its isolation; and complex extraction and counter-current distribution procedures yielded 40 μg. of the compound per 100 g. pineal.[4] Its structure, confirmed by synthesis, proved to be N-acetyl-5-methoxytryptamine,[4] a derivative of 5-hydroxytryptamine:



This compound is biologically unique. Although administered 5-methoxytryptamine has been shown in the laboratory animal to be metabolised to 5-methoxyindoleacetic acid,[5] no endogenous methoxylated indole had been identified until Lerner et al.[6] isolated 5-methoxyindoleacetic acid, a biologically inert substance, from bovine pineal; presumably this is a metabolite of melatonin, which was characterised soon afterwards.[4] The major metabolic pathway, at least in the rat, is via 6-hydroxylation to N-acetyl-5-methoxy-6-hydroxytryptamine [7]—a detoxication mechanism which may prove of considerable interest, for there is some reason to suppose that 6-hydroxylation of an indole is associated with an increase in hallucinogenic activity.[8]

In the past, methoxylation of a biologically active amine has been associated with curtailment of its function. Thus, 3-methoxylation of catechol amines is now thought to be the major physiological inactivation mechanism in man and laboratory animals.[9] It is therefore intriguing to find a compound in which the substitution of a methyl group causes such pronounced potentiation of activity,

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which is greatest when the N-acetyl group is also present.[10] Weissbach and Axelrod [11] have now identified a highly localised specific enzyme—5-hydroxyindole-0-methyltransferase—in the pineal region of the cow and monkey, which transfers a methyl group from S-adenosylmethionine to N-acetyl-5-hydroxytryptamine. They achieved a twentyfold purification and showed that it was quite distinct from other methyl transferring enzymes.

Despite the apparent absence of this methyltransferase activity in sites other than the pineal, Lerner et al.[12] found small amounts of a substance with the characteristics of melatonin in peripheral nerves of man, monkey, and cow. This led them to speculate whether melatonin might play some part, as do most of the other known lightening agents, in the transmission of nerve impulses. It may also be important in the pathogenesis of malignant melanoma or vitiligo.[13] The findings in peripheral nerve are so far the only direct data on man; but human pineal gland contains very high concentrations of 5-hydroxytryptamine [14]—the melatonin precursor.

Whatever the outcome of the melatonin story, it has focused the attention of biochemists on the function of the pineal gland.[15]

PROGNOSIS OF THE EYE SIGNS OF GRAVES' DISEASE

A GOOD deal is now known about the biochemistry of hyperthyroidism (though its underlying cause still eludes us), but the mysterious eye changes which often accompany it remain as enigmatic as anything in medicine. Sir Russell Brain [16] has usefully summarised what little is known about exophthalmos and the other eye signs of Graves' disease, and concluded that no single known factor can be the sole cause. Hyperthyroidism as such cannot be primarily responsible, since exophthalmos can (and often does) advance at the very time when hyperthyroidism has been brought under control by medical or surgical means. Nor can the thyroid-stimulating hormone (T.S.H.) be the only causal factor, since blood-levels of this hormone are most consistently raised in spontaneous myxœdema, in which exophthalmos is never found. Yet, though neither thyroid nor pituitary hormones are likely to act in isolation, these cannot be excluded as possible factors in the production of exophthalmos.

In such an obscure condition treatment is inevitably empirical and its effects uncertain. Brain recommends that hyperthyroidism, when present, should be treated, and in severe cases he recommends tarsorrhaphy, irradiation of orbit and pituitary, and surgical decompression as necessary. He has not been impressed by the effects of hormonal treatment. No measure applied at an early stage of progressive exophthalmos can be relied on to prevent worsening of the eyes.

Although treatment is unsatisfactory, at least prognosis should be possible. This demands knowledge of the long-term history of the disease, which hitherto has not been available. Now, however, Hales and Rundle [17] have made a quantitative study of 104 patients with Graves' disease, whose eyes were carefully measured at the beginning and end of a fifteen-year period. Three aspects of the ocular manifestations were studied separately: exophthalmos, ophthalmoplegia, and lid retraction. In 75 patients exophthalmometer readings were unchanged; in 24 exophthalmos had increased; and in 5 it had decreased by more than 2 mm. Thus, judged by objective measurement, the actual protrusion of the eyes usually remained unchanged, but was more likely to increase than to decrease. Ophthalmoplegia remained unchanged in about two-thirds of the patients, increased in 6, and decreased in 4. In this respect, the score was about "all square". Spastic retraction of the upper eyelids ("lid retraction"), on the other hand, disappeared in 60% of those who showed this sign initially, and decreased in most of the remainder. Since lid retraction makes the eyes appear to protrude (even when they do not actually do so), and is responsible for a great deal of the ocular disfigurement in Graves' disease, its notable tendency to disappear with time led to a great improvement in the appearance of the patients' eyes. Thus in the series as a whole most patients felt that their eyes were much better, although objective measurements of exophthalmos and ophthalmoplegia showed either no change or deterioration. Hence in advising patients with the ophthalmic manifestations of Graves' disease they may justifiably be told that the appearance of the eyes will improve with time. This is a great help to their morale, which usually needs all the support the physician can give.

Discussing these findings, Hales and Rundle support Pochin's [18] suggestion that the factors responsible for initiating exophthalmos may be quite different from those which maintain it over long periods. Pochin suggested that the initial protrusion might be permitted by weakness of the extrinsic eye muscles; this would leave a space in the orbit behind the eyeball, and a neat experiment in rabbits showed that spaces in the body are commonly filled by fat. A hypothesis of this sort would account for Rundle and Pochin's [19] finding of an excess of fat in the orbit in most cases of Graves' disease, whether or not eye signs had been recognised during life.

The clinical course of the eye lesions, although unpredictable in detail, usually conforms to the same general pattern. A period of fairly rapid progression, lasting a few months, is followed by a very much longer period when the eye signs remain essentially static. There is danger to the eyes only during the initial phase of progression, and it is then that the difficult decision has to be made whether radical measures should be applied. Once the eyes have become stabilised they are no longer in danger, but may remain a source of great embarrassment to the patient. Fortunately the eyes tend to look less conspicuous with the passage of time, even though objective measurement shows no decrease in the actual degree of protrusion.

Sir HENRY TIDY, consulting physician to St. Thomas's Hospital, died on June 3 at the age of 82.

Dr. G. W. H. TOWNSEND has been elected president of the Society of Medical Officers of Health for 1960–61.

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Occasional Survey

RECENT ADVANCES IN THE BIOCHEMISTRY OF PSYCHOSIS

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I SHALL here discuss some aspects of recent work on the biochemical basis of psychosis, firstly reviewing the present state of our knowledge, and secondly considering the best methods of research in the immediate future.

Recent Research in Biochemical Psychiatry

Two years ago I suggested (Smythies 1958) that progress had been made because various workers had reported positive features in the metabolism and physiology of schizophrenics which differentiated them from normal people. Most of these claims have since had to be abandoned, but the evidence which was presented in support of the two main hypotheses of the ætiology of schizophrenia will now be considered in the light of the fresh evidence.

The Adrenochrome Hypothesis

In support of this hypothesis Hoffer and his associates (see Hoffer and Osmond 1959) had claimed that adrenochrome and adrenolutin are psychotomimetic agents, that adrenochrome is a normal constituent of the blood, and that schizophrenics show a decreased ability to destroy injected adrenochrome as compared to normal controls.

Unfortunately the experiments which are supposed to show that these compounds are psychotomimetic are unconvincing, because, in most cases, no double-blind controls were used. Thus the results may well have been due to placebo effects, the extraordinary range of which was not fully realised at the time. Hoffer's only experiment using such controls produced negative results (see Smythies 1958). Furthermore Heath (1959a) and Pfeiffer (1959), who both tested pure adrenochrome in a dose of 50 mg., observed no effects. von Taubmann and Jantz (1957) also reported that pure adrenochrome is inactive, and their further claim that some unspecified oxidation product of adrenochrome is active does not exclude the possibility of placebo effects. Schwarz et al. (1956) observed no psychological or behavioural effects from 75 mg. of adrenochrome given intravenously, though they claim to have seen increased paroxysmal activity in depth recordings from the brains of two schizophrenic patients. This evidence is unconvincing, however, as insufficient records are presented, too few subjects were tested, and no quantitative control was used.

Thus whether these agents produce a condition resembling psychosis remains uncertain. The only properly designed trial so far conducted has yielded negative results, and the balance of evidence suggests that these agents are not psychotomimetic, at least when given by ordinary routes. We have, of course, no means of knowing what such chemically reactive compounds might do if released by some metabolic fault in the brain, but there is as yet no evidence that this happens.

Feldstein (1959) has alleged that Hoffer's claims of detecting adrenochrome in the blood and cerebrospinal fluid of normal people were based upon an unfortunate artefact in his method. Thus Feldstein sees no reason to doubt the findings of Szara et al. (1958), using another method of analysis, that adrenochrome is *not* a normal constituent of blood.

Disturbed Adrenaline Metabolism in Schizophrenia

The original hypothesis, put forward by Harley-Mason (1952), was that methylation of the phenolic groups of adrenaline might somehow be concerned in the genesis of schizophrenia. Five years later Axelrod (1957) discovered that o-methylation is in fact the main method of normal metabolism of adrenaline. Hence it seemed possible that disorders of this methylation process might occur in schizophrenia, and this idea led to two investigations. Firstly the examination of adrenaline metabolism in schizophrenia (Resnick and Elmadjian 1956, Cohen et al. 1959, Resnick et al. 1958) disclosed no differences in adrenaline metabolism between schizophrenics and normal controls, either in the proportions and amounts of the various methylated metabolites or in the rates of utilisation of adrenaline or noradrenaline. Secondly, mescaline analogues were studied (see below).

Although adrenaline metabolism in the brain may be affected in psychosis (for the metabolism of injected adrenaline could well be different from that produced endogenously) there is no proof of this.

Minz (1960) has reviewed the effects of schizophrenic serum on the " cortical epinephrine pressor response ".

If adrenaline is placed on the exposed cerebral cortex of the rabbit, a rise of blood-pressure ensues; but, if the rabbit is pretreated with schizophrenic serum this effect is abolished or even reversed. This does not happen if the serum used is from normal people or from people under stress. Even more interesting is the finding that, in animals pretreated with schizophrenic serum, the adrenaline and noradrenaline levels in the hypothalamus are raised significantly when compared with rabbits treated with normal serum. The level of adrenaline was raised eightfold, and that of noradrenaline twofold. The serotonin levels were unaffected.

These results will be of the greatest significance if they can be confirmed.

The Serotonin Hypothesis

Recently a number of workers have been unable to show any abnormality of serotonin in psychosis.

Feldstein et al. (1959) concluded from their measurement of 5-hydroxytryptamine levels in the blood and of 5-hydroxyindoleacetic acid (5-H.I.A.A.) excretion in the urine that there is no evidence, as yet, to link defects in serotonin metabolism with schizophrenia. These workers emphasised the great hour-to-hour variation in the amount of 5-H.I.A.A. in the urine and the lack of dietary controls in most studies of this kind. Brengelmann et al. (1959), having previously shown (1958) that 5-hydroxytryptophan (5-H.T.P.) alleviates the psychological effects of lysergic acid diethylamide (L.S.D. 25), demonstrated that 5-H.T.P. did not alleviate the schizophrenic psychosis. They thus failed to confirm the hypothesis put forward by Woolley and Shaw (1954) and a related concept by Gaddum (1954), that a naturally occurring substance resembling L.S.D. 25 is concerned in the genesis of schizophrenia.

Toxic Factors in Plasma

Bergen et al. (1960) using quantitative methods of evaluation have confirmed previous reports (Winter and Flataker 1958) that plasma—but not serum—from schizophrenic patients is significantly more toxic to rats and mice than is plasma from normal controls. Moreover they have shown that, because the toxic factor will diffuse across a semipermeable membrane if a protein carrier is present on the other side, it must be a small molecule. This finding is not specific for schizophrenia as the toxic factor is present in other types of mental illness, but the schizophrenics may be reacting abnormally to this compound, as suggested below.

Melander and Martens (1959) claim to have confirmed Heath's (1959b) work with taraxein by animal experiments. Their findings, although qualitative and not quantitative in design, are clear, and may be summarised thus:

Taraxein, prepared from schizophrenic plasma by a modification of the original method of Heath et al. (1957) was injected intravenously into rhesus monkeys. These developed "catatonic-like symptoms" within fifteen minutes. The injection of a psychotomimetic phenothiazine called 'Kabi 888' in a small dose (2–3 mg. per kg. body-weight) produced no obvious effect. But, when Kabi 888 was given fifteen minutes after the dose of taraxein that itself produced only slight catatonia, immediate and complete loss of muscle-tone, general pilo-erection, and deep sleep were produced—effects quite unlike the ordinary taraxein reaction. The coma lasted for fifteen minutes, and then the ordinary taraxein reaction returned. During the coma the electroencephalogram showed abnormalities. Inactivated taraxein and the fraction prepared from normal plasma had no effect. When L.S.D. 25 was substituted for the taraxein the results were the same. Adrenolutin (20–25 mg. per kg. body-weight intravenously) given to monkeys had little effect by itself. But pretreatment with taraxein or L.S.D. 25 produced muscular relaxation and coma. This effect of L.S.D. 25 was shared by aceytl-L.S.D. (psychotomimetic), but not by brom-L.S.D. (not psychotomimetic).

Melander and Martens suggest that taraxein and L.S.D. 25 may enable certain drugs, injected intravenously, to act upon brain centres which are not normally accessible to them. These workers also suggest that endogenous low-molecular compounds in the blood might produce behavioural changes through the same mechanism. For instance, one could speculate that the presence of taraxein in the blood of the schizophrenic might render the brain susceptible (possibly by some action on the blood-brain barrier) to the toxic effects of the non-specific plasma constituent of low molecular weight described above. This hypothesis could easily be tested experimentally.

In this context I was able to show, by statistically evaluated quantitative methods, that adrenolutin (itself without any behavioural effect) reduces the excitatory effect of L.S.D. 25 on mice (Smythies 1959). This finding is compatible with those of Melander and Martens if we suppose that reduction of excitation and the production of flaccidity, sleep, and eventual coma are in some degree similar.

Moya et al. (1958) showed that extracts of schizophrenic urine produced a statistically significantly greater degree of hypoglycæmia in rabbits than did extracts from the urine of normal controls or other mental patients. The same extracts were also more toxic to rabbits.

These findings provide a promising basis for future work, if they can be confirmed. The chemical identification of taraxein or of the plasma fraction studied by Bergen et al. (1960) and Winter et al. (1958) would be discoveries of major importance.

Indoles in Schizophrenia

Indoles.—From time to time abnormal indoles have been reported in schizophrenic urine. But Rodnight's recent work (Rodnight and Aves 1958) probably explains why. Thus, some mentally ill subjects, particularly depressives, excrete an excess of skanonyl sulphate in the urine, but the level of excretion bears no relation to their clinical state, and it can be reduced to very low figures by giving antibiotics by mouth, without alteration in their clinical condition. Other bacterial decomposition products of tryptophan also are sometimes found. Rodnight thinks this is probably because a slower rate of intestinal peristalsis in these patients leads to increased bacterial decomposition of tryptophan in the gut, but factors affecting the intestinal flora have not been excluded.

Indole bases.—When the excretion of serotonin and tryptamine (which are the only indole bases found in urine [Rodnight 1956]) was measured in 20 schizophrenics and 20 depressives the values were normal. By the method used other indole bases could have been detected, but none was found. A special search was made for bufotenin and N-methyl tryptamines by a modification of the method capable of detecting as little as 3 mμg. per ml. urine, but with negative results.

Indole acids.—Rodnight found no abnormality in the excretion of indoleacetic acid or 5-H.I.A.A. in groups of mentally ill people. Occasional subjects excreted some 5–10 times the normal amount of indoleacetic acid but this was found to be intestinal in origin.

Adenosine Triphosphate and Glucose Metabolism

Gottlieb et al. (1959) reported changes in adenosine triphosphate turnover in schizophrenics, but this was based on only 13 cases, and the results are expressed as means without standard deviations or statistical control. The raw data varied so much that their conclusions are unlikely to be valid. These same workers (Frohman et al. 1960b) have recently produced more convincing evidence, from adequately designed experiments, that schizophrenic plasma contains a factor that interferes with the control of carbohydrate metabolism.

This factor prevents the decrease in the proportion of glucose converted to ribose, by means of the hexosemonophosphate shunt, that is normally brought about by insulin. Thus the schizophrenic metabolism is relatively inflexible when tested by insulin, and it cannot change its ratio of glucose metabolised for energy to glucose metabolised for synthetic purposes under these conditions, as the normal metabolism can. Further experiments (Frohman et al. 1960a) showed that chicken red blood-cells incubated in schizophrenic plasma had a higher lactate/pyruvate ratio than had those incubated in plasma from normal controls. This suggests the presence of some inhibitor of aerobic metabolism in the plasma of schizophrenics, which may affect some phase of hydrogen transport.

Serum Cæruloplasmin Levels

Studies at the National Institutes of Health (McDonald 1958) have failed to confirm previous reports that serum-copper levels and plasma-oxidase activity are raised in schizophrenics. McDonald showed that the previous results were really due to a dietary deficiency of ascorbic acid amongst the schizophrenic population, and his results have been confirmed by Aprison and Drew (1958), Frohman et al. (1958), and Edelstein et al. (1959).

Tryptophan Metabolism

Price et al. (1959) recently reported that 6 out of a total of 19 schizophrenics metabolised *l*-tryptophan abnormally along the kynurenine pathway.

Excessive amounts of kynurenic acid, o-aminohippuric acid, acetylkynurenine, kynurenine, and hydroxykynurenine were excreted (after ingesting tryptophan) as compared to normal controls. These changes were also shown by patients with porphyria and other psychoses. Patients with neurological diseases, however, had normal tryptophan metabolism. Confirmation of these findings is eagerly awaited.

The Outlook for the Future

During the past ten years research into the biology of schizophrenia has greatly increased. But the results of all this work are a collection of negative findings that do not themselves contribute to knowledge of a positive kind, as well as a large series of contradictory reports. There is now widespread agreement (Benjamin 1958, McDonald 1958, Kety 1959) that work in this field needs new and stricter criteria of design, with much closer controls.

Better orientation of research is also needed. As McIlwain (1959) has said:

"Until the central problems of neurochemistry have been successfully tackled and we see more clearly how the nervous system utilizes its large energy supply in nervous transmission . . . and how the brain is moulded to an animal's experience, chemical aspects of most of the neurological sciences—and above all, material approaches to nervous, mental and emotional diseases—remain as empirical as was organic chemistry before the advent of structural formulæ."

There is widespread agreement that more emphasis should now be placed on basic neurochemical and neuropharmacological research to produce a groundwork of fact upon which to base more adequate biochemical studies in the clinical field in the future. This type of research has the added advantage that, whatever the outcome, positive contributions to scientific knowledge will be made. But innumerable problems must be tackled in neurochemistry and neuropharmacology, most of which, presumably, will be irrelevant to the problems of psychiatry. How, then, can we choose those that may be relevant?

One of the most promising leads in this field is the investigation of the mode of action of the psychotomimetic drugs—particularly mescaline and its near relative amphetamine. These are both closely related to physiological substances, and they produce the best simulation of the naturally occurring psychoses. Clearly, if we knew the precise action of these drugs we should be able to submit the metabolism of schizophrenics to much more penetrating tests. A start has been made at the Worcester Foundation (Smythies and Levy 1960) where the effect of all available analogues of mescaline have been investigated, using the Winter and Flataker (1958) rat rope-climbing test.

3 : 4 dimethoxyphenylethylamine has only half the activity of mescaline (3 : 4 : 5 trimethoxyphenylethylamine). Replacement of the methoxy group in the 4 position by a hydroxy group abolishes all activity where its replacement by a benzyloxy group increases activity. Benington et al. (1958) showed that a series of methyl-substituted phenylethylamines produced rage reactions in cats.

At present very little is known about the way that mescaline works in man. Block et al. (1952) showed that very little mescaline ever reaches the brain; hence it may produce its effects by interfering with the metabolism of some other substance—e.g., adrenaline—in the body. The new metabolite of mescaline discovered by Harley-Mason et al. (1958) is a close chemical relative of vanilmandelic acid, a major metabolite of adrenaline. But the fate of 60% of mescaline when ingested by man remains unaccounted.

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Special Articles

IRRADIATION AND MARROW TRANSPLANTATION
STUDIES IN COOPERSTOWN

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DURING the past 4 years marrow transplantation in irradiated patients, and marrow and kidney transplantation in irradiated dogs, have been studied at the Bassett Hospital in Cooperstown, New York, by a research group working with the cooperation and assistance of members of the departments of medicine, surgery, pædiatrics, radiology, and pathology.[1–20] In the first year marrow

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transplantation by intravenous infusion of fresh or glycerol-frozen marrow from volunteers, cadavers, or fœtuses was assessed in leukæmic patients receiving whole-body exposure to air doses of 100–600r X-irradiation.[1] The irradiation was increased to 600–1200r (6 12) of cobalt-60 gamma-ray in the 2nd year, and to 1200–2000r in the 3rd year. In the last two groups exposures were continuous at 0·5–2r per minute. Pilot studies were made in dogs at exposures up to 2400r at 18r per minute.

Nineteen patients with acute leukæmia and one with chronic leukæmia in relapse were treated.

Of these, five will not be discussed, since they were seriously infected and beyond hope. Of the others, six went home improved in remissions lasting 2–6 months. Eight died 1–4 weeks after irradiation, without satisfactory re-establishment of marrow function, and usually with pneumonia and capillary pulmonary hæmorrhages. One went home unimproved.

Of the six patients who recovered, one with chronic leukæmia in relapse had been given 450r followed by frozen cadaver marrow. Evidence of temporary graft function was obtained.[1] The patient had a partial remission of 6 months. Two patients had autogenous return of normal marrow function within 4–5 weeks of irradiation. One of these had 325r and then fresh adult marrow.[6] Autogenous marrow recovery was evident after 4 weeks, and then remission lasted 6 months. The second patient received 1100r followed by frozen fœtal hæmopoietic tissue (livers and spleens*) and fresh adult marrow.[18] Autogenous marrow recovery was evident after 5 weeks, and remission lasted 2 months. Neither patient showed evidence of survival of the attempted marrow grafts.

In addition four patients with normal identical twins were irradiated with 850, 1140, 1600, and 2000r and were then given infusions of fresh marrow from the normal twin.[12 19] All showed evidence of returning marrow function within 2 weeks, in contrast to the 4–5 weeks already described as necessary for evidence of autogenous return.

The twin who received 2000r had a severe intestinal syndrome, but seemed well on the way to recovery at the end of the 2nd week. Jaundice of undetermined ætiology appeared in the 3rd week after irradiation, and the patient died on the 20th day. The peripheral blood and the bone-marrow showed evidence of partial marrow recovery. The other irradiated twins with leukæmia went home feeling well and in complete remission, but their remissions lasted only for 2–3 months. One, a girl of 5 years, who was given 850r, lived for 15 months. During that period she is said to have shown no adverse effect from her radiation exposure.

Finally a patient in relapse, given 400r and an infusion of his own normal marrow (stored during remission), recovered from the acute effects of irradiation and went home but without evidence of remission.

Discussion

Our conclusions are that radiation is helpful in some patients with leukæmia; that autogenous marrow function after exposures of 300–1200r returns slowly, requiring 4–5 weeks for regeneration; that infusion of isologous marrow from an identical twin is followed by prompt marrow recovery even after exposures of 1600–2000r; that the intestinal syndrome that followed 2000r at 2r per minute points to this being about the limit of general radiation exposure after which survival can be made possible by marrow replacement in man.

* Kindly supplied by Dr. H. E. M. Kay of the Royal Marsden Hospital, London, S.W.3.

These conclusions are partly supported by studies in dogs. Autogenous regeneration of marrow after dogs have been exposed to near-lethal general radiation is slow, taking 4–5 weeks.[20] Marrow recovery after successful transplantation—either isologous or homologous—is brisk, taking 1–2 weeks.[3 9 13] Fatal gastrointestinal complications—bloody diarrhœa and perforation—are likely after continuous exposures in excess of 1800r at 5r per minute.

Evidence of successful transplantation of homologous marrow is usually seen in dogs after radiation exposures in the 800–2000r range. On the other hand, experience in man at high-dose ranges has been limited. Evidence of transplantation of fresh homologous marrow was seen in one patient after 1200r. Another, after 1600r, showed no evidence of transplantation. These patients were both leukæmic. Neither survived more than 3 weeks, and the relation of their disease to their clinical course and transplantation experience is uncertain.[19]

When transplantation of homologous marrow is successful in the dog, and probably also in man,[21 22] the problem of secondary disease and the graft versus host reaction, with its lymphoid and nutritional disturbances, is formidable but not necessarily overwhelming.

With symptomatic treatment several dogs have survived these disturbances and regained normal health.[20] One, now alive and well, shows continued evidence of graft survival a year after an exposure of 1800r. Another with a successful marrow graft also received a kidney transplant from the marrow donor.[15] The kidney functioned normally, and after removal of the dog's own kidneys, the transplant carried successfully the entire load of nitrogen exertion. After being clinically normal for 2 months this animal fell victim to one of the intercurrent illnesses which are common during the period of secondary syndromes, and it died of thrombocytopenia and pneumonia on the 73rd day after irradiation. This was 39 days after removal of its own kidneys, and there was no evidence of nitrogen retention.

The difficulties and high mortality-rates from secondary disease in irradiated dogs successfully transplanted with homologous marrow contrast strikingly with the essentially benign clinical course of irradiated dogs that have been infused with samples of their own normal marrow kept for 2–96 hours at 4°C in tissue-culture media, or stored for longer periods in glycerol at −80° or −180°.[13 17 20]

In these animals normal lymph-node histology and immune responses, as well as bone-marrow function, return rapidly.[13] Probably in consequence the dogs do remarkably well both immediately after irradiation and in later months. No dog in a group of fifteen exposed to 800–1500r has died of intercurrent endemic canine disease, been seriously ill, or shown after a year signs of late radiation damage. After exposure to 1000r, one has recovered potency and sired a litter of four normal pups.

Theoretically a similar benign course might be expected in irradiated patients treated by infusions of fœtal hæmopoietic tissue.[10] To date, however, our efforts to transplant such tissue—either fresh or frozen, in man or in dog—have met with no success, for reasons that require further evaluation. Our intention is to continue a cautious exploration of these and related problems of marrow and kidney transplantation [23] after high dosage of general radiation both in dogs and in selected patients.

This work was supported by research grants (A-2215, C-2643, and A-2473) from the United States Public Health Service, and the Atomic Energy Commission Contract AT (30-1)-2005, and by the John A. Hartford Foundation.

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In England Now

A Running Commentary by Peripatetic Correspondents

IN these days, when everything is known already, it is difficult for a researcher to find a worthwhile topic. Perhaps this lack of meaning in life is why there is so much preoccupation with statistical significance. At all events, statistics is in Medicine to stay, and with it has come the ubiquitous "P". Clearly, "P" is better as a servant than as a master and we must not be scared of it. The important thing is to know how an apparently hostile "P" can be made into a friend.

Suppose you have discovered an association between X and Y. You publish a series of cases of Y in which a surprisingly high proportion (it seems to you) are also suffering from X. The paper is entitled "X-ic Y: a New Syndrome?" or "An-X-ic Non-Y-ism" or simply "X and Y in Egregious Lapsang Multips". It is not long before some fellow researcher, resting between ideas for the time being, writes in caustically to say that as the association is not significant ($P > 0.001$) he, for his part, has the gravest doubts as to the reality of the syndrome. Now, there is a riposte available to you. Having first made sure that your association is significant at a much lower probability, say, $P = 0.05$ (and it nearly always will be) you reply as follows:

"It should be more widely understood that the figure following 'P' represents the estimated probability that the two features would be found in association as often as in fact observed, by sheer chance. When 'P' is small one can say with relative confidence that the association observed was *not* due to chance. It is merely a matter of confidence; and if Dr. Q— is not prepared to take odds of 20 to 1 on, but demands the ludicrously outside odds of 1000 to 1, then all I can say is, Dr. Q— has my sympathy and should take a long and restful holiday to get his nerve back."

Statistics plays an increasingly important part in the more emotionally involved fields of Medicine, and in these controversies the trick never fails.

* * *

"First the little nurse with the squeaky shoes came along with a tray of things. 'Just a prick, Mrs. Melville,' she said. She had a go at one arm and then tried the other. She went gently at it but it hurt just the same. 'You've got awfully small veins, Mrs. Melville,' she said, 'I'll have to ask sister to do it.' 'Well, what's all the bother about, nurse?' said the sister, and she stuck the needle in hard and pushed it about inside a bit. 'Well, would you believe it?' said the sister, 'you *have* got difficult veins, Mrs. Melville! Nurse, please ring for Dr. Smallweather and then prepare the instrument trolley. He may have to cut down.'"

* * *

"Remove the two wing nuts" it said in the car handbook, "and the panel bulbs will then be accessible." Usually, when anything goes wrong with the car I place it with all speed and a few remaining shreds of confidence in the hands of my garage man. But this was just a little green bulb on the dashboard that wouldn't light up, and so, regardless of the untimely end of Belloc's Lord Finchley, I started to tackle it myself.

The first snag was that there weren't any wing nuts to be seen. I put my hand up behind the fascia, and immediately became entangled in an absolute cat's cradle of tubes and wires. However, the wing nuts were there, and by treating the first one with all the delicacy which I would lavish on a gangrenous retrocæcal appendix, I managed to get it out. I had just got the second one to the end of its thread when my finger slipped, and the nut disappeared into the depths with a cascade of little clatters, rather like one of those little steel balls on a fairground machine that go round and round and round and then (appropriately enough) vanish into a hole marked "Lost".

By the time I had explored all the sharp-edged recesses behind the dashboard, dismantled the steering-column casing, and taken up the carpets, it was getting dark; so I put them all back again. I removed the instrument panel, found I still couldn't get anywhere near the bulb for the green light, replaced the panel, and fixed it with the one remaining nut. The first time I stopped the car next day the missing nut was sitting smugly on the parcel shelf.

When I went humbly to the garage they said it wasn't the bulb at all, and when they had fitted a new contact-switch the green light stayed on all the time. This, they said, was something nasty to do with the big ends. So now, although I don't really qualify, I shall be doing what Lord Finchley ought to have done after all.

* * *

The milk-cart rattled down the road and our Liz, a keen gardener, ran out with bucket and spade in search of treasure trove. "You can't have that, Liz—I saw it first," piped the lady next door, "and anyway it's outside my house." But Liz had beaten her to it. "A clear infringement of manoorial rights," commented the lawyer across the road when he heard of the incident.

* * *

Gift-bearing Greeks are always suspect and so are gift-bearing neurotic patients. One should be wary of the parcel sent to one's home or left in the consulting-room, especially in the course of treatment. It is an invariable sign of failure. Psychiatric successes are marked by the absence of gratitude either verbal or in kind.

Not all patients progressing indifferently will "buy one off" with presents, but those who do are of interest. Usually the presents are ostentatious, but cost the patient little in cash or effort. One suspects that they are prizes won at carnivals, discarded Christmas and birthday presents, the surplus of some sport or industry, or the products of a "do-it-yourself" hobby. An author will send you an autographed book, a farmer a chicken, a fisherman a cut of salmon, a confectioner a tin of sweets. If by chance an expensive or well-chosen present arrives, it has come from a patient who was diagnosed as "not psychiatric" and referred to a surgical or gynæcological colleague for appropriate physical treatment. By then they have moved into an atmosphere where tangibly expressed gratitude is traditional.

Can this phenomenon be linked with the fact that no-one ever gives money to mental hospitals? Is the mind meaner than the body after all?

* * *

Simon had a little pocketmoney unspent after his seventh birthday celebrations. It was suggested to him that he should open a savings account. He agreed, and accompanied by his mother presented himself at the post-office, where the clerk greeted him as an old friend.

"I want to start a Post Office book. Here's a pound."

"Put it there, Rothschild. How old are you?"

"Seven."

"When were you seven?" And having asked if Simon could write and whether he understood the questions on the form, the clerk handed it over.

Simon proceeded to fill it in without a smudge or blot, but my wife thought it proper to look it over before it was handed back. A good thing too, for the entry under the heading of "occupation" was certainly not legally recognisable. He had merely written "tree climbing."

* * *

If I had sat in Dunfermline town,
Drinking the blude-red wine;
If Sir Patrick had been Sir William,
Sailing a ship o' mine;

Half-owre, half-owre to Aberdour,
And fifty fathoms deep,
The Spens report and the broken ship,
Might lie at each other's feet.

Letters to the Editor

DEATHS FROM LUNG CANCER

SIR,—Dr. Hulme points out (May 28) that the ratio of male to female deaths from lung cancer in 1958 was "considerably greater" than the ratio in 1948 (deaths from respiratory cancer). If smoking is the cause of lung cancer and if more women are now smoking than used to, then he would expect the ratio to decrease rather than increase. "What," he asks, "have the statisticians to say?"

In reply, the statisticians would advise him not to rely upon crude death-rates at all ages. If he will compare the changes which have occurred between 1949 and 1958 at *different ages* he will find the following ratios of the male to the female death-rate (the figures for 1948 are distorted since they include mediastinal tumours).

Age in years..	15–24	25–34	35–44	45–54	55–64	65–74	75 and over
1949	6·5*	2·3	4·0	8·2	8·0	5·4	3·6
1958	1·4*	2·1	3·5	6·8	9·7	9·8	6·0

* Based upon less than 30 deaths in each sex.

In short, at ages under 55 years the death-rates of women have risen nearer to those of men; at ages above 55 they have increased much less rapidly than those of men.

Statistics published by the tobacco industry show that the cigarette consumption of women was negligible before 1920 and even twenty-five years ago (1935) it was still less than 10% of the consumption of men. In 1958 it had risen to 40%. Given, on the average, a long latent period between first exposure to a respiratory carcinogen and the clinical appearance of cancer, the sex changes in mortality at different ages are not incompatible with the sex changes in smoking. We would guess that the crude sex ratio used by Dr. Hulme, and its resulting paradox, will continue to rise for some years yet.

Statisticians on both sides of the Atlantic, we may add, had not overlooked the paradox, and Dr. Hulme will find it discussed at greater length in the literature than is possible in a reasonably short letter.

London School of Hygiene and Tropical Medicine, London, W.C.1. A. BRADFORD HILL
RICHARD DOLL.

ANHIDROSIS AND HEATSTROKE

SIR,—The recent reports by Bannister [1] and by my good friends Sargent and Johnson in your issue of May 7 [2] emphasise the complexity of anhidrosis. The sudden cessation of sweating during exposure to heat, as described by Bannister, was familiar to those of us working on climatic problems during the war,[3] and I have frequently noticed it since. This stoppage might be either general or local and was usually precipitated by some interference—e.g., if an arm was washed and dried to get a good sample of sweat at a particular time, sweating would sometimes stop on that arm. This phenomenon, which was never formally reported, suggests that when the sweating mechanism is interfered with it can easily be put out of order. Clinically it appears that anhidrosis comes on after a final insult to overworked sweat-glands. The final insult may be miliaria ("prickly heat") when it comes on slowly, or it may be from local trauma, as from drying the skin, when it comes on acutely; and undoubtedly there are many other "insults" as well. Which were operative in Bannister's and in the American cases it is impossible to say.

1. Bannister, R. *Lancet*, 1959, ii, 313, and personal communication.
2. Sargent, F., Johnson, R. E. *ibid.* May 7, 1960, p. 1018.
3. Ladell, W. S. S. *Brit. med. Bull.* 1947, **5**, 5.

Sargent and Johnson report that their subjects when on a predominantly carbohydrate regime gave a diuretic response to water even when on a restricted water intake; this is not surprising, for even quite severely dehydrated subjects will "waste water" in this way.[4] What is more interesting is that subject 8T on a mixed diet providing 2000 kg. calories per day not only showed a water diuresis when he was in water debt but also developed, after drinking, a transient pitting œdema. Such observations emphasise that the disorder is systemic rather than local for all its predominantly local manifestation; the diuresis and the œdema also point at least in the direction of the posterior pituitary and the adrenal cortex. Similar pointers were seen in the cases of anhidrosis described by Waterlow and myself.[5] These men were deficient in water and salt yet could not retain either. Similar cases were described by Horne and Mole,[6] but whereas their cases responded normally to antidiuretic hormone (A.D.H.) ours did not. There was similar conflicting evidence in the case of the adrenal hormones; three of four cases treated with deoxycortone responded with increased salt retention, but the fourth failed to respond. These observations, coupled with the suggestion for which there is some evidence [7] that A.D.H. partially suppresses heavy sweating, are the basis for the following working hypothesis.

Undoubtedly under the conditions in which anhidrosis occurs there will be considerable secretion of A.D.H. and of aldosterone; it is possible that with the increasing amount of A.D.H. the renal tubules become less and less responsive ("failure of the target organs") which would account for the diuresis; but meanwhile the sweat-glands would continue to be inhibited in part or in whole by A.D.H.; at the same time the adrenal cortex is fully active and it is possible that it might pass into the "state of exhaustion", partly from the thermal stress, partly from any other stress there may be—e.g., traumatic, nutritional, or infectious. The clinical picture and the response to treatment will obviously depend upon the stage at which the condition is seen. Initially the renal tubules may still give some response to A.D.H.—hence Horne and Mole's observations. The sudden outburst of sweating reported by Sargent and Johnson on rehydration might be due to the suppression of A.D.H. secretion and the consequent release of the sweat-glands from inhibition. Local changes cannot entirely be excluded; there may be blocking effects from the miliaria, and reflexes of the type described by Ferres [8] are probably also involved. There is not sufficient experimental evidence to confirm my hypothesis, but I have suggested that it does indicate the experimental and clinical observations that require to be made.[9]

Sargent and Johnson call attention to my observations that a rise in body temperature can cause the cessation of sweating, but they do not accept this as part of the ætiology of heatstroke. I have observed this falling off in sweat response (the ratio of sweat-rate to rise in rectal temperature) on many occasions in both Africans and Europeans. The falling off is exponential, and at a rectal temperature of 102°F (38·9°C) the response is so diminished that the total amount of sweat being produced is less than that produced at 100°F (37·8°C) even though the stimulus is greater. Even slight rises in temperature are paid for by a falling off in sweat response: thus men resting in heat before working sweat less than men who start work immediately with a lower initial body temperature.[10] Sargent and Johnson suggest that this could not be the basis of heatstroke because symptoms of heatstroke develop after sweating stops. What do they mean

4. Ladell, W. S. S. *ibid*, p. 1.
5. Ladell, W. S. S., Waterlow, J. C., Hudson, M. F. *Lancet*, 1944, ii, 491, 527.
6. Horne, C. O., Mole, R. H. *ibid.* 1949, ii, 279.
7. Ladell, W. S. S. *S. Afr. J. med. Sci.* 1948, **13**, 145 and unpublished observations.
8. Ferres, H. M. *J. Physiol.* 1958, **143**, 39P.
9. Ladell, W. S. S. Paper read at 6th International Congress on Tropical Medicine and Malaria, Lisbon, 1958.
10. Ladell, W. S. S. *Trans. R. Soc. trop. Med. Hyg.* 1957, **51**, 189.

by symptoms? If they refer to coma then the answer was given by the late Eugene DuBois who pointed out that the brain can withstand body temperatures up to 105°F [11]; the sweat response does not approach zero until a temperature of about this level is reached. If they refer to the rise in body temperature then I think we are back at the old question: which came first, the hen or the egg?

Sargent and Johnson also quote me as reporting that sweating is diminished by dehydration; they do not, however, point out that I failed to find any such diminution until at least 2·5 litres of body water had been lost, which is nearly a 4% loss of body-weight; and even then the diminution was by no means pronounced.[12] It is a little difficult from their article to decide whether they accept the effect of dehydration on sweating or not; personally I doubt if it is of major significance.

Chemical Defence Experimental Establishment,
Porton, Down,
Salisbury, Wilts. W. S. S. LADELL.

BLINDNESS IN WEST AFRICA

SIR,—In an editorial two years ago [13] doubt was cast as to whether onchocerciasis was a major cause of blindness or not; three workers were concerned in the argument that it was not. The survey reported in my book demonstrates conclusively the opposite view, no matter how you may pontificate (May 28, p. 1196). If you are right, then an awful lot of people are wrong in Europe, Africa, and America, where the reviews have been entirely favourable; and if the view that this disease is not responsible for very much blindness is right, it will be the first time in the history of medicine that " everybody is out of step except my Johnny ". Your reply to my previous letter obscures the truth. Thus we must disagree.

Nuneham Courtenay,
Oxon. F. C. RODGER.

SELECTION OF BREAST-CANCER PATIENTS FOR ADRENALECTOMY OR HYPOPHYSECTOMY

SIR,—In their article of May 28, Dr. Bulbrook and his colleagues claim that the response to adrenalectomy and hypophysectomy for metastatic breast cancer can be predicted from determination of urinary 17-hydroxycorticosteroids (17-OHCS) and ætiocholanolone. They suggest that these estimations indicate the hormonal environment in which the tumour is growing and that this is related to the possibility of a remission after operation.

Before surgeons throughout the country start worrying their biochemical colleagues to undertake ætiocholanolone estimations, which are extremely laborious, an alternative explanation of the findings may be worth considering.

Bulbrook, Greenwood, and Hayward found that a high ratio of urinary 17-OHCS/ætiocholanolone is associated with a poor response to operation and vice versa. 17-OHCS are the urinary metabolites of hydrocortisone secreted by the adrenal cortex. In illness they are maintained at a normal level although in severe illnesses they may rise above normal. Ætiocholanolone is the main 17-ketosteroid in the urine and these are the excretory products of adrenal androgens. Adrenal cortical secretion of androgen is maintained in mild illness but is greatly reduced in chronically ill patients. The ratio 17-OHCS/ætiocholanolone is therefore high in seriously ill debilitated subjects, and lower in patients whose general condition is well maintained.

An alternative explanation of the findings of Bulbrook, Greenwood, and Hayward would be that very sick patients are less likely to respond to major endocrine surgery than those whose general condition remains fairly good. It is to be hoped that the clinicians in this group will make an independent assessment of the preoperative states of these patients to examine this possibility.

London, W.1. J. D. N. NABARRO.

BLOOD-GROUP DISTRIBUTION TO BE EXPECTED IN PERSONS TRISOMIC FOR THE ABO GENE

SIR,—The condition in which one chromosome in the normal complement is represented three times (trisomy) instead of twice is already known to be a cause of two congenital abnormalities in man—Klinefelter's syndrome and mongolism. Trisomy is theoretically possible for any one of the 22 pairs of autosomes in man. In addition there are four possible types of trisomy for the sex chromosomes (XXX, XXY, XYY, and YYY), making a total of 26 trisomics. Many of these (such as YYY) will be lethal at a very early intrauterine stage.

It remains possible, however, that the two known cases, mongolism and Klinefelter, are not the only viable trisomics. I have therefore thought it worth considering the possibility of a third kind of trisomic, for the chromosome carrying the blood-group gene ABO. This would produce a characteristic change in blood-group frequencies. The change would be the same if only that part of the chromosome carrying the ABO locus were trisomic.

If p, q, and r are the frequencies of the three alleles, O, A, and B in a randomly breeding population, the Hardy-Weinberg law predicts the frequencies of the various diploid genotypes. The frequencies expected for OO, OA, OB, AA, AB, and BB are given by the terms in the expansion of the expression $(p+q+r)^2$. To extend this law to the trisomic condition one merely has to substitute the expansion of $(p+q+r)^3$ for that of $(p+q+r)^2$.

The expected frequencies of the trisomic genotypes OOO; OOA, OAA, AAA; OOB, OBB, BBB; OAB, AAB, ABB, will then be: p^3; $3p^2q$, $3pq^2$, q^3; $3p^2r$, $3pr^2$, r^3; $6pqr$, $3q^2r$, $3qr^2$, in that order.

Of the ten genotypes the only one which can be recognised on blood-group alone is the homozygous recessive OOO, with a frequency of p^3. The other phenotypes are represented by 3 genotypes each. This is particularly worthy of note in the case of the AB phenotype which has only 1 possible genotype in the diploid.

Let us now see how this would affect the blood-group frequencies in a given population. The normal (diploid) blood-group percentages in the Manchester region of the Blood Transfusion Service are given in the table below:

	Blood-group percentages				*Gene frequency*		
	O	A	B	AB	p	q	r
Diploid ..	48	41	8	3	0·69	0·25	0·06
Trisomic ..	33	50	9	8			

From these I have estimated p, q, and r, which in turn have been used to estimate the blood-group percentages in a trisomic population. Note the greatly reduced incidence of group O, the somewhat higher incidence of group A, and the more than doubling of group AB, which is the greatest relative change. The detailed effects of the trisomic condition will vary between populations according to the gene frequencies, but one can make the general prediction that relative to the diploid population there will be a decrease in group O and an increase in group AB.

It follows that any disease caused by trisomy for the ABO chromosome would have a blood-group distribution differing in a characteristic manner from the general population in which it arose. This is one means by which a statistical correlation between blood-group and disease could be brought about. I do not think that such an explanation has hitherto been considered.

A blood-group distribution very similar to that expected in such a trisomic population has recently been found in children's tumours arising in tissues of ectodermal origin.[1] These tumours are mostly gliomas, the rest being retinoblastomas and tumours of the sympathetic nervous system and epithelium.

11. DuBois, E. F. Fever and the Regulation of Body Temperature. Springfield, Ill. 1948.
12. Ladell, W. S. S. *J. Physiol.* 1955, **127**, 11.
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In this sample of 131 tumours, χ^2 with 3 degrees of freedom for deviation from the expectation in a diploid population was 14·91, with $P < 0·01$. The $\chi^2_{(3)}$ for deviation from the trisomic expectation was only 5·77 with $P < 0·2$. Other tumours in children (259 in number, mainly leukæmias and sarcomas) showed a normal blood-group distribution ($\chi^2_{(3)} = 3·19$, $P = 0·4$).

In a survey of many kinds of tumour such results might arise in an entirely fortuitous way. That that explanation is not appropriate in this instance is shown by corroborative evidence from a much larger survey by Yates and Pearce [2] of astrocytic gliomas. The situation was somewhat complicated by the restriction of the anomalous blood-group distribution to cases diagnosed since 1945, but Steward's sample was also of recent date (1953–58). Yates and Pearce found a large excess of A over O and also an excessive number of ABs. For the 309 astrocytic gliomas since 1945 the deviation from the control blood-group distribution was highly significant ($\chi^2_{(3)} = 17·9$, $P < 0·001$), whereas there was good agreement with trisomic expectation ($\chi^2_{(3)} = 6·3$, $P = 0·1$).

It was also found (Steward, personal communication) that 51 survivors of retinoblastoma (the only malignant tumour of ectodermal type with a high survival-rate) showed an excess of group A, though the χ^2 was not significant.

If trisomics for any chromosome survived to birth they would be likely to have a severe disability which would appear early in life if not congenitally, like children's tumours. In addition, trisomics for the ABO chromosome would have the same blood-group distribution as children with ectodermal tumours. If a trisomic were fertile, he would be expected to pass the extra chromosome to half his offspring, and the condition would then be inherited like a dominant gene mutation. When retinoblastoma is familial it is in fact transmitted in this way.

Thus it would seem desirable to establish by direct cytological observation whether children with gliomas or other ectodermal tumours are trisomics. If they should prove to be so it would be natural to conclude that the trisomic chromosome was the one carrying the ABO locus, and we should have achieved for the first time the identification of a human autosome with a genetic marker.

I wish to thank Dr. J. K. Steward and Dr. P. O. Yates for their assistance with data and criticism of the manuscript.

Cytogenetics Laboratory,
Christie Hospital and Holt Radium Institute,
Manchester. A. J. BATEMAN.

PERIPHERAL VASCULAR DISEASE TREATED BY AMNION IMPLANTATION

SIR,—In your issue of March 12 you published a further article by Mr. Troensegaard-Hansen on amnion implantation. I am surprised that there has been no comment in your correspondence columns on this procedure, as I have come to regard it as one of those rare gems in the catalogue of surgery of which it may truly be said that it *never* does any harm and *may* do a great deal of good.

I have carried out amnion implants in some fifteen cases during the past nine years with the result that one third have been "excellent", one third "improved", and one third "no change". The cases were nearly all referred because the physician or surgeon in charge had failed to produce improvement by any other means, and the degree of severity varied between group II and group III.

It has been said that because the modus operandi of the procedure is not understood it should not be taken seriously; but I, personally, believe that patients should have the chance of benefiting from any otherwise harmless treatment whether it actually works by auto-hypnosis or a general hormonic reshuffle!

I have also used amnion as a surface dressing on many occasions and find that in selected cases it is both quicker and better than Thiersch grafting. I think, however, that the most important single factor in its use either superficially or by implantation is the selection and preparation of the membrane itself, and unless this is carried out strictly according to the technique formerly described by Troensegaard-Hansen then results will be disappointing. I do, on the other hand, differ from him in operative technique in so far as all my implants have been carried out through a half-inch incision under local anæsthesia in outpatients.

London, W.1. JOHN E. BUCK.

2. Yates, P. O., Pearce, K. M. *Lancet*, Jan. 23, 1960, p. 194.

OTOTOXICITY OF NEOMYCIN AEROSOL

SIR,—I was disturbed to read Mr. Fuller's report of May 7 of ototoxicity due to neomycin aerosol therapy in two children. Dr. Young's letter of May 28 is certainly reassuring. I have used neomycin aerosol inhalations for nearly 100 patients with chronic respiratory infection in the past 3 years, and some of these have continued the treatment for more than a year. The effect on the infection appears to have been less definite in many patients than that obtained with oral tetracycline treatment, but there has been no evidence as yet of ototoxicity, and I had come to regard the treatment (perhaps prematurely) as safe in this respect.

I should like, however, to take this opportunity of reporting a case of severe ototoxicity following weekly intrapleural neomycin instillations (1 g. dose) in a patient with a bronchopleural fistula and secondarily infected tuberculous empyema. The tinnitus was first reported after the 4th week. It would appear that considerable absorption of neomycin had occurred from the pleural space.

The Hartley Hospital,
Colne, Lancs. W. H. HELM.

SOME UNCRITICISED ASSUMPTIONS IN PSYCHIATRIC THOUGHT

SIR,—In his article of March 19 Dr. McConaghy helps to expose the unrecognised sadism which is the basis of the dynamic method of psychiatry.

We are shown how the patient is subjected to continuous "interpretations", really nothing but criticisms of the patient's character and whole way of life, which effectively destroy his self-confidence as well as stimulate a resentment towards the therapist, which cannot be expressed without embarrassment, because the therapist seems not to be attacking the patient's character, but only helping the patient in an objective fashion. The psychiatrist is shown to be a "passive-aggressive" type, unaware of his own aggressions, and unable to assume any responsibility for generating hostility in the patient, all of which, he assumes, misguidedly, is merely a reflection of unresolved childhood conflicts.

Dr. McConaghy's deftly written article is valuable in that it demonstrates how a therapeutic method can be, and certainly often is, made to serve destructive ends in the hands of the wrong type of person. That psychoanalytic methods are *intrinsically* the expression of "passive aggression" is Dr. McConaghy's main point, however, and this assertion cannot really be taken seriously. All psychiatric training centres recognise as clearly as Dr. McConaghy that persons with hostile or defensive characteristics should be discouraged from the practice of psychiatry. Furthermore, it is a well-established principle of dynamic psychiatry that interpretations cannot be effective if the patient experiences them as criticisms or if they are forced upon him. In fact, the ideal situation for psychotherapy is one in which, in an accepting atmosphere, for most patients a novelty, the patient becomes able to discover his own blind spots unaided.

Dr. McConaghy's article is entertaining to read but, unfor-

tunately, poorly informed, and will only serve to reinforce popularly held misconceptions about the real purposes of psychiatry.

Tufts University School of Medicine,
Boston, Mass. RICHARD SCHWARTZ.

URINE OR LIQUOR AMNII?

SIR,—It is not uncommon for patients to be admitted during the antenatal period with possible premature rupture of the membranes, but following admission it is difficult to decide whether the fluid leaking is urine or liquor. It is often a simple matter to decide between the two by placing an 'Albustix' (Ames Company) on a sanitary towel which has been worn by the patient until it has become damp.

By folding the sanitary towel over and squeezing the albustix the latter will show a positive reaction for protein if the dampness is the result of liquor amnii, whereas it will give a negative reaction with urine, unless the urine contains much albumin. There is the possible error of vaginal discharge, which might also give a positive reaction for protein, but such a discharge is usually quite obvious and not difficult to distinguish between the other two conditions.

I find this test clinically useful, and it is, of course, based on the fact that the protein content of liquor amnii approximates to that in blood plasma.

General Infirmary,
Salisbury. M. R. FELL.

PREVENTION OF TETANUS

SIR,—Dr. Fulford's article and your leader in the issue of May 21 called attention to a serious problem. I have been concerned by the increase in the number of cases of serum sickness, due to A.T.S., being seen in my department. There is an increasing opinion in the profession that all patients who are given A.T.S. should be offered active immunisation six weeks later. The problem is—who should offer this immunisation? I am informed that the public-health authorities are only authorised by the Ministry of Health to use tetanus toxoid in the "triple vaccine". In practice therefore they are only able to offer protection against tetanus to infants and children. I am thus now endeavouring to arrange for immunisation to be offered at the hospital. As we give an average of seventy prophylactic A.T.S. injections a week it will be necessary to create a special clinic for the purpose.

It is essential that all those immunised should carry some indication to this effect. At present the only persons I presume to be immunised are those who have been in the Armed Forces. Parents of immunised children rarely know if the vaccine used included tetanus toxoid. At this stage it becomes apparent that this is a national problem and that it must be tackled on a national scale by the Ministry of Health. Not only should immunisation be offered to all age-groups but it is essential that a foolproof method of indicating that immunisation has been done must be devised. From my experience of diabetics in hypoglycæmic coma, the carrying of a card indicating their disability is more honoured in the breach than in the observance. I agree with your suggestion that the only reliable indication would be a small and universally accepted tattoo sign.

I hope that your leader and the discussion it has provoked on this subject will come to the notice of the Ministry of Health and stimulate appropriate action. Until this action is taken it is incumbent on all using A.T.S. to see that the patients who receive it are offered active immunisation afterwards. In this way we may begin to reduce the morbidity caused by the widespread injection of horse serum.

Casualty Department,
St. James' Hospital,
London, S.W.12. DAVID CARO.

THE CAUSE OF ŒDEMA IN "COR PULMONALE"

SIR,—May I comment on the interesting suggestion of Dr. Campbell and Dr. Short (May 28) that œdema in "cor pulmonale" may be due to the effect of hypoventilation on renal reabsorption of sodium bicarbonate. It is the rise in pCO_2, and not the fall in pH, which is effective in promoting bicarbonate reabsorption; it might therefore be more appropriate to speak in this context of "hypercapnia", and not of "respiratory acidosis", as they do in their summary. The relief of œdema which some patients with cor pulmonale obtain with acetazolamide (whose effect is to lower both pCO_2 and pH) may support the point which I have raised—and also, of course, the general contention of their paper.

Department of Medicine,
The Royal Infirmary,
Manchester. D. A. K. BLACK.

BACK PAIN AND HYPERÆSTHESIA

SIR,—Dr. Glover (May 28) has drawn attention to a condition of the spine in a most commendable manner. As a result I hope that medical colleagues will pay more detailed attention to the spine and to the value of manipulation.

There is no doubt that he describes what the osteopaths have been talking about since the beginning of the century—the osteopathic spinal lesion. Dr. G. Macdonald and Dr. W. Hargrave-Wilson in their book *The Osteopathic Lesion* (1935) described the condition as an acute or chronic joint strain. Dr. James Mennell in his *The Science and Art of Joint Manipulation* (1952), described it as a "joint bind". My own definition in my *Manual of Osteopathic Technique* (1959) is a "condition of impaired mobility in an intervertebral joint".

Surely we are all trying to describe and evaluate the same phenomenon. That these lesions exist there is not a shadow of doubt, but because they are difficult to demonstrate in any other way than by clinical observation, they have been missed except for a few medical men and the osteopaths and chiropractors.

The very fact that it was the unorthodox practitioners who first attempted to describe the lesion has been the cause of delay in its recognition as a clinical entity. Furthermore, terminology has confused the issue, and explanations offered by osteopaths have not been acceptable medically.

In spite of unsatisfactory theoretical considerations the practical application has not been lacking. If Dr. Glover cares to glance at my book he will see detailed methods of examination which will make his tests more specific, and accurate manipulative procedures are described to correct the lesions.

By using mobility X-rays it is possible sometimes to show the restricted range of movement, and after manipulation to show the increased range, but as Dr. Glover says, the size of the joints makes radiographic evidence difficult to procure and more difficult to evaluate. I must have done hundreds of mobility films to try and demonstrate the movement fault in these lesions, yet I have only one or two which will stand up to critical analysis.

It is important that these lesions are recognised early, not only to save the patient a good deal of pain but to help prevent chronicity in these joints. It is easy for symptoms to subside without restoration of movement because adjacent joints can take over their range. I am myself convinced that these minor joint lesions more often than not do persist and, with their restricted mobility, lead on to degenerative changes and in due course to disc pathology.

Let us deal with these relatively minor lesions in their early stages and treat them effectively with accurately localised manipulation and so prevent present pain and future pathology.

London, W.1. ALAN STODDARD.

SIR,—Dr. Glover deals with a sorely neglected subject. However, although agreeing wholeheartedly with the points he makes, I feel bound to point out that the back

syndrome described is no other than the osteopathic lesion which has been recognised for many years. While this expression may be anathema to members of the profession there is no doubt that the syndrome he describes has been appreciated and treated successfully for many years by registered osteopaths and others. It seems strange therefore that such a common complaint costing so many man-hours should attract so little interest and so often receive negative and unsatisfactory treatment from the qualified doctor.

St. Thomas' Hospital, London, S.E.1. T. M. MITCHELL-FOX.

EFFECT ON THE KIDNEY OF DRUGS CONTAINING PHENACETIN

SIR,—The results reported by Dr. Harvald and his colleagues (Feb. 6) on the effect on the kidney of drugs containing phenacetin do not in my opinion substantiate the claim that 4-chloroacetanilide is chiefly responsible for the quantitative change in the urinary sediment and hence for kidney damage.

Apart from criticisms of the interpretation of the results, there are two objections to the method of comparing the three types of phenacetin. Firstly, each patient received only one type of phenacetin; to eliminate the possibility of differing patient reaction it is surely advisable to compare the three types of phenacetin in the same patients. One has only to look at the next article by Dr. Sleight in the same issue to see criticism of work where drugs were not compared in the same subjects. Secondly, the results for the control or treatment periods of all patients in each series were averaged for comparison purposes. Since the initial red blood-cell counts vary from nil to 9·4 million and the patient response is variable, this is not considered a reliable method of assessing the effect of the different treatments. If one treats the results of each patient individually there seems to be no necessity for using logarithmic values which tend to give a distorted picture.

Certain measurements of the red blood-cell count are obviously in error, such as the one of the second day of treatment of patient no. 5. Discarding five such measurements the mean values of the red-cell counts for each patient during both the control and treatment periods may be calculated. Examination of these mean values indicates a greater preponderance of increases in blood-counts of treatment periods over control periods in the case of phenacetin containing 4-chloroacetanilide than with pure phenacetin. However, if the mean values are arranged in three equal groups of patients covering initial blood-counts (millions) of (*a*) 6·0–1·2, (*b*) 1·0–0·4, and (*c*) 0·3–0·1 (see table) one finds that 6 out of 9 patients in group (*a*) were receiving pure phenacetin and 8 out of 9 patients in group (*c*) were receiving phenacetin containing 4-chloroacetanilide. Thus, each series in the investigation did not have a random allocation of patients.

MEAN VALUES OF RED CELLS (MILLIONS)

Patient	Control period	Treatment period	Increase (+) or decrease (−) with treatment
	Group (*a*)		
5	6·0	4·1	−1·9
17	5·8	3·8	−2·0
1	5·5	5·0	−0·5
2	4·2	2·7	−1·5
7	2·9	4·0	+1·1
27	2·8	4·5	+1·7
9	1·9	1·9	0
12	1·9	1·6	−0·3
4	1·2	2·9	+0·7
	Group (*b*)		
22	1·0	1·5	+0·5
3	0·9	2·2	+1·3
13	0·9	1·7	+0·8
8	0·7	1·5	+0·8
10	0·7	0·6	−0·1
14	0·5	1·3	+0·8
6	0·5	0·3	−0·2
15	0·5	0·9	+0·4
18	0·4	0·4	0
	Group (*c*)		
26	0·3	0·5	+0·2
11	0·2	0·6	+0·4
19	0·2	0·6	+0·4
21	0·2	0·5	+0·3
23	0·2	0·2	0
16	0·1	0·4	+0·3
20	0·1	0·1	0
24	0·1	0·2	+0·1
25	0·1	0·2	+0·1

Moreover, in group (*c*), 7 out of the 9 patients showed an increased count and the other 2 had unchanged counts whilst in group (*a*) 5 patients showed a decrease, 3 showed an increase, and 1 showed no change. Examination shows that the increases and decreases of mean red-cell counts with treatment within groups (*a*), (*b*), and (*c*) have a normal distribution about their mean. Thus the evidence suggests that the incidence of increase in the red-cell count with treatment is associated not with the presence of 4-chloroacetanilide in the phenacetin but with the values of the initial blood-cell count—being proportionately greater for the smaller initial values.

In the case of the white-cell counts a similar exercise shows that 7 out of 11 patients registered an increase on treatment with phenacetin, 6 out of 8 patients an increase on treatment with phenacetin containing 0·13% 4-chloroacetanilide, and 4 out of 8 patients an increase when treated with phenacetin containing 0·3% 4-chloroacetanilide. There would not appear to be a significant difference between these three series of treatments. Even the interpretation of the results by the method of Harvald et al. is not convincing. It is not sufficient to argue that "the patients in the last series (treated with phenacetin containing 0·3% 4-chloroacetanilide) had better renal functions than the first two series". No such difference exists in the red-cell counts, and if there were such a marked difference this particular series of patients should have been split between all three methods of treatment.

There would seem to be no basis therefore for ascribing changes in urinary sediment to 4-chloroacetanilide at the levels used in this investigation.

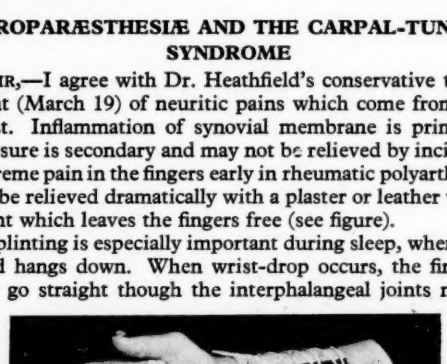
The *British Pharmacopœia* limits the 4-chloroacetanilide in phenacetin to 0·17%. Presumably careful consideration was given in fixing the limit to ensure that this content of 4-chloroacetanilide is innocuous when phenacetin is taken under any conditions except those of violent abuse.

Gobowen, Shropshire R. P. W. KUP.

ACROPARÆSTHESIÆ AND THE CARPAL-TUNNEL SYNDROME

SIR,—I agree with Dr. Heathfield's conservative treatment (March 19) of neuritic pains which come from the wrist. Inflammation of synovial membrane is primary; pressure is secondary and may not be relieved by incision. Extreme pain in the fingers early in rheumatic polyarthritis can be relieved dramatically with a plaster or leather wrist splint which leaves the fingers free (see figure).

Splinting is especially important during sleep, when the hand hangs down. When wrist-drop occurs, the fingers may go straight though the interphalangeal joints never



have been arthritic. In many patients wrongly diagnosed as scleroderma, the thickened condition is secondary to arthritic wrist-drop. There is usually a long history of attacks of pain and swelling of the wrist.

Institute of Rheumatology,
East Melbourne, Victoria. MICHAEL KELLY

MOTHER'S UNION

SIR,—The letter from "The Widdicombe File" last week says that the responsibilities of the pathologist include the training of medical laboratory technicians.

As a medical laboratory technician of mature years, whose feelings are also altruistic concerning the College of Pathology, I challenge this statement. The medical laboratory technician has to qualify under his own steam, to a great extent. The majority of pathologists are satisfied to get a technician using his hands, rather than his head, who will become a member of the conveyor-belt system of present-day pathological investigations.

The training of medical laboratory technicians is left almost entirely to the more keen type of technicians themselves, who, with the cooperation of local education authorities, have organised courses for the benefit of those technicians who wish to prepare for the intermediate and final examinations of the I.M.L.T.; and—let us face the facts—these senior technicians also assist greatly in training pathologists. Perhaps this is a good argument in favour of "The College", so that when a junior pathologist does take up an appointment he will know at least some of the techniques required in a medical laboratory, and not have to watch the technician who, because he is a decent fellow, teaches his boss his job.

I heartily agree with the correspondent when he says that the worst training centres for medical laboratory technicians are the well-known medical schools, which look on these technicians as "the fetch-and-carry brigade".

I should welcome the day when the pathologist could honestly say he was responsible for the training of medical laboratory staff, as it would lessen the need for such as myself for nightly sedation, trying to organise next session's syllabus of lectures for the keen future technicians who wish to qualify in medical laboratory technology—a job that has been my lot for the past fifteen years, a job which all pathologists in the area appreciate, but none accepts as part of his responsibility (according to the Widdicombe correspondent).

St. Helens, Lancs. WILLIAM STIRRUP.

HYPOGLYCÆMIA ASSOCIATED WITH SARCOMA

SIR,—Like Professor Butterfield and his colleagues (March 26) we were intrigued to read of Dr. Stern's hypothesis that the hypoglycæmia which developed in our patient (Jan. 23) might be due to excessive aminoacid production by the tumour in a leucine-sensitive individual. If our patient were leucine-sensitive it should still be possible to produce a fall in blood-sugar by performing a leucine test-meal.

The patient, who has been in good health since her operation, with no evidence of recurrence and no further hypoglycæmic episodes, kindly agreed to be admitted to hospital where a leucine test-meal was performed. 15 g. (0·15 g. per kg.) of L-leucine was given orally in the fasting state and blood-sugar estimations were performed at intervals over the next 90 minutes. The results were as follows:

Fasting	113 mg. per 100 ml.	60 min.	107 mg. per 100 ml.
30 min.	112 " "	90 min.	99 " "
45 min.	104 "		

These figures show a slight fall, probably due to the fasting state, but there is no evidence that leucine, in this dose, has had any effect on the blood-sugar. The patient remained well throughout the test and had no hypoglycæmic symptoms.

It seems unlikely therefore that Dr. Stern's hypothesis obtains in this particular case, but it would certainly be worth while testing any similar cases in this way in the future.

We are much indebted to Dr. Joyce Baird, of the Department of Therapeutics, University of Edinburgh, for her help with this case.

Midwifery Department,
Foresterhill, Aberdeen. M. C. MACNAUGHTON
E. A. F. PRIEST.

"SPIRITUAL HEALERS" IN HOSPITAL

SIR,—Dr. V. Cotton Cornwall, as president of the Regional Hospitals' Consultants and Specialists Association, has written to the medical press (*Lancet*, May 28) criticising the permissions granted to spiritual healers to attend the sick in hospitals (under special circumstances), and I therefore assume he has presented his strongest case against this new practice.

His first argument is that the Bishop of Lichfield said that the Churches' Council of Healing does not recognise the National Federation of Spiritual Healers. Does this comprise a valid objection? The Federation is undenominational and its constitution prevents its affiliation with any other religious bodies. The gift of healing can never become the prerogative of any religion, and certainly not that of the Churches' Council of Healing. To suggest that healers should be debarred from helping the sick, because the Churches' Council does not recognise us, is surely the weakest of arguments.

Dr. Cotton Cornwall next raises the point that the act of a doctor giving permission for a spiritual healer to attend his patients may lay him open to a charge of "covering". We have taken a Queen's Counsel's advice on this matter, and it is his opinion that the granting of such permission does not violate the rule of "covering" or "association", neither does it imply acceptance by the doctor of the efficacy of spiritual healing.

Those are the only objections mentioned by Dr. Cotton Cornwall, but he adds that members of the National Federation "should not be given special privileges, nor granted consultations with the medical staff."

We are not asking for special privileges. Spiritual healing is part of our common religious belief. It is a divine act. Therefore the attendance of a spiritual healer upon a patient has the same significance as that enjoyed by ministers of religion, who visit the sick for the purpose of prayerful intercession and the laying-on of hands. That is all we wish to do.

We are not asking for consultations with the doctors as a right or privilege. Surely there can be no harm in a doctor, if he wishes, talking about a patient's condition with a healer, any more than when he discusses this with the patient's relatives or friends. It seems that some doctors are trying to create difficulties when there are none, and inventing suppositionary circumstances which may never arise.

The main objection seems to be that we healers shall be giving a spiritual healing "treatment". Of course we shall; but let us get this in its right perspective. We say that a divine power or healing force is transmitted to the patient through our gift of healing. There is abundant evidence to prove that this is so. Surely this is what the members of the Churches' Council of Healing seek too. The difference is that the healer possesses the gift of healing, and unfortunately the average parsons do not. Why deny to those patients who desire to benefit in this way the help that we can give? Spiritual healing treatment is not in opposition to medical practice—on the contrary, it will assist the patient to respond more readily to it.

On behalf of our Federation, I thank you for the kindly references in your editorial, concerning the sincerity and integrity of our membership and recognising that we have no ulterior motives or desire to upset medical ethics. You conclude by saying that when one of our members attends a

patient, the other patients may think that he has the sanction of the hospital for what he does. May I suggest that we should not allow " what other patients think " to be a valid reason for denying spiritual healing to those who desire it—and there are always the screens if needed.

Guildford, Surrey. HARRY EDWARDS
President, National Federation of Spiritual Healers.

SIR,—I hope I shall be allowed to welcome your annotation of May 28 on " spiritual healers " in the wards, and to express some astonishment that, in this age, such a regressive step should be contemplated by some hospital management committees. Is there perhaps some disparity between the intellectual and emotional development of these, and the general body of medical opinion? It was Bernard Shaw who provocatively expressed the opinion that all conceptions were immaculate; certainly there must be few who would not hold that all healing is spiritual. However, this is not to say that, in the movements going by the names of " spiritual healing " and " faith healing ", lie practical and theoretical dangers, both of naivity and esotericism. Surely the art of healing is best left in the hands of the doctors, who are fully aware of the primacy of faith and confidence, and the ministers of the great religions, with whom they share the care of the patient's well-being. If indeed the " spiritual healer " with his laying of hands is to be allowed the run of the hospitals, why not the chiropractor, the neuropath, the yogi, and the witch doctor?

London, W.1. S. CHARLES LEWSEN.

SIR,—I think I can bring some reassurance to those who are concerned to the fact that a number of hospital management committees have been unwise enough to grant access to spiritual healers.

I understand that this concession is always subject to the approval of the consultant in charge of the case. On demanding whether they would allow such access to their own patients in the wards, the consultant reply I have invariably received has been, " over my dead body."

Esher, Surrey. I. S. MACDOUGALL.

CHOLESTEROL DETERMINATION BY THE ZLATKIS METHOD

SIR,—Polyunsaturated fatty acids can interfere [1] with the determination of cholesterol by the procedure of Zlatkis et al.[2]

Vannini and Del Vecchio [3] compared the Zlatkis method with that of Abel et al.[4] and found that the normal discrepancy of about 7% became greater (21%) when jaundice was present (correlation coefficient between serum-bilirubin and % difference = +0·7).

In jaundice there is also an increase of biliary salts in blood which may interfere with the development of the H_2SO_4–$FeCl_3$ colour in the Zlatkis reaction.

Some biliary salt solutions become coloured if treated with H_2SO_4-$FeCl_3$. In fact:

1 mg. of the Na-salt of the acid:	*gives an optical density of:*
cholic	1·097
glycocholic	0·699
desoxycholic	0·393
taurocholic	0·155

It is not therefore advisable to use the Zlatkis method for the determination of cholesterol in serum or body fluids of jaundiced patients because of the higher readings which are accounted for not only by the high bilirubin levels but also by the increased level of bile salts in the serum or body fluids.

Istituto Ganassini, Milan. A. DEL VECCHIO.

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KEROSENE POISONING

SIR,—The recent correspondence on kerosene (paraffin) poisoning prompts me to inquire whether any of your readers has had experience in treating these cases with anti-inflammatory steroids. There are several references in the literature to corticosteroid therapy being useful, and even lifesaving, in the chemical pneumonitis arising from oxides of nitrogen,[1] crude oil,[2] and aspirated stomach contents.[3] Since kerosene appears to exert a major portion of its toxic effect through such a chemical pneumonitis, steroid therapy seems worth a trial.

Haskell Laboratory for Toxicology and Industrial Medicine, E. I. du Pont de Nemours & Company, Wilmington, Delaware. G. J. STOPPS.

DIAGNOSIS OF POLYMYOSITIS

SIR,—The increased use of muscle biopsies in recent years has permitted the recording of many interesting observations. If, however, these findings are to be applied in the diagnosis of disease and the recognition of new disease entities, great caution must be exercised lest newly discovered changes in familiar diseases be considered sufficient justification for claiming the discovery of a new malady. Still more should we be on our guard against forcing into one group, on the basis of a single histological or group of histological appearances held in common, conditions which have been separated in the past by painstaking clinical observation. Indulgence in such uncritical reasoning is likely to discredit a valuable method of investigation and delay what might otherwise be a rapid advance in medical knowledge.

Nowhere in the field of neuromuscular disease is such caution more necessary than in regard to " polymyositis ", and we must be grateful to Dr. Heathfield and Dr. Williams for bringing this matter into the open in their paper of May 28.

Under the heading of polymyositis they group 28 cases varying in age from 5 to 77 years. Some of these cases had evidence of collagen diseases (rheumatoid arthritis, lupus erythematosus); others had a carcinoma; still others resembled cases of muscular dystrophy. What then was the feature which induced Heathfield and Williams to present these cases as examples of a single disease entity? It appears to have been the presence of muscular wasting with a distribution suggesting muscular dystrophy, together with a muscle biopsy showing either focal necrosis or diffuse inflammation or both, or again, alternatively or as well, the discovery of different areas in the same muscle giving electromyograms typical of myopathies and of denervation, or of myopathic areas alone in which case there would be a strength-duration curve indicative of denervation. Unfortunately their biopsy findings are not given in detail but it is evident that in many—perhaps half—of their cases cellular infiltrations were absent or only of slight degree. In this regard it must be remembered that Dr. J. G. Greenfield and his coworkers,[4] in a relatively small series of muscle biopsies, were able to report 3 cases of *familial* proximal muscular syndromes in which there was gross leucocytic invasion and in 2 of these cases there was floccular degeneration and phagocytosis. These cases were presumably examples of muscular dystrophy and we may ask ourselves whether we are doing a service to medicine by calling such cases polymyositis on account of these histologi-

1. Von V. Lachnit. *Zbl. Arbeitsmed.* 1958, **8**, 177.
2. Graham, J. R. *Trans. Amer. clin. climat. Ass.* 1955-56, **67**.
3. Marshall, B. M., Gordon, R. A. *Canad. anæsth. Soc. J.* 1958, **5**, 438.
4. Greenfield, J. G., Shy, G. M., Alvord, E. C., Berg, L. An Atlas of Muscle Pathology. Edinburgh, 1957.

cal changes. Dr. S. Nevin has also, in a recent communication to the Royal Society of Medicine, called attention to this same point.

In the remaining cases reported by Heathfield and Williams the lesions in the muscles in 3 cases were described as sarcoid-like without further details, while the remainder showed focal necrosis which was often confined *to a single fibre or part of a fibre*. Even apart from the mildness of these lesions, floccular or cloudy-granular change—which would probably correspond to Heathfield and Williams' focal necrosis—was shown by Greenfield and his collaborators to be present in all their 4 cases of familial muscular dystrophy in childhood with a duration of four years or less. If therefore the changes described by Heathfield and Williams can be present in indisputable cases of familial muscular dystrophy, we may ask ourselves whether some of the adult cases may not also be late muscular dystrophies or purely degenerative conditions, the cause of which remains undetected. It is true, and Greenfield admitted this, that there are cases with large nodular aggregates of leucocytes, but their cause is unknown and the wisdom of grouping them with conditions which have an affinity to the collagen diseases is debatable. Cases where there is a primary and indisputably inflammatory reaction in muscle without disease of other tissues would therefore seem to be much rarer than Heathfield and Williams would suggest.

Difficult though the task of interpreting muscle biopsies from this type of patient may be, surely the interpretation of electrodiagnostic data must be still less certain; since, although the electromyographer is able to detect the inability of a patient to bring motor units or parts of motor units into action, he is quite unable to determine the nature of the lesion or whether it affects the terminal motor axons or the muscle-fibre. Little wonder that the group of electrodiagnostic features put forward by Heathfield and Williams as indicative of " polymyositis " have been found by Dr. P. Bauwens to occur in peripheral neuritis and motor-neurone disease.[5–7] Thus we are dealing with a condition more difficult to diagnose with certainty even with the help of electrodiagnosis and muscle biopsy than was thought a few years ago. But even should one feel bold enough to make this diagnosis, would one in fact be doing more than saying this is a patient with cancer or a collagen disease or neither, who has wasting of the proximal limb and trunk muscles produced by one of a number of different mechanisms as yet unknown to us?

Walton and Adams [8] in their book on polymositis report 40 cases of this " disease " which represented their personal experience (which included access to the files of the Massachusetts General Hospital) over a period of more than twenty years. 6 of these cases were of carcinomatous myopathy, 20 showed evidence of collagen disease, and 14 formed a heterogenous group of great interest but of such variability in age of onset and symptomatology as to make one doubt whether even in this one group the patients were suffering from the same disease. These authors performed an important service in showing that patients with the same histological changes in the muscles could suffer from such various diseases, and we would do well to remember that the repertoire of histologically demonstrable reactions of muscle is small. To recognise that carcinoma may be associated with changes in the muscle resembling those seen in muscular dystrophy and in collagen disease constitutes an advance, but to imply that these patients are all suffering from one disease—polymyositis—is in my view a retrograde step.

While not denying that there are many diseases affecting muscles rather than their nerves, and which differ in their natural history from the classical muscular dystrophies, would it not be better at this stage to follow Greenfield and report only what we see and not introduce a new name which as often before will form a favourite but quite misleading diagnosis?

The Midland Centre for Neurosurgery, Holly Lane, Smethwick. A. L. WOOLF.

5. Bauwens, P. *Proc. R. Soc. Med.* 1954, **47**, 918.
6. Bauwens, P. *ibid.* 1955, **48**, 194.
7. Bauwens, P. *Amer. J. phys. Med.* 1959, **38**, 109.
8. Walton, J. N., Adams, R. D. Polymyositis. Edinburgh, 1958.

RECTAL EXAMINATION

SIR,—Time and again in your journal attention has been drawn to the valuable aid given to diagnosis by digital examinations of the rectum; in fact, I believe Osler stated that a consultant physician was one who did this examination when other physicians had failed to do it.

I feel the examination is often neglected in people's homes because of the difficulty in disposing of a rubber glove. For this reason I should like to draw attention to a plastic disposable finger-stall with a hand-guard made by Down Brothers. This finger-stall is always clean and the hand is adequately guarded—and it is disposable. All of which can be got for a trifling cost.

New Cross Hospital, Wolverhampton, Staffs. KENNETH HAZELL.

HISTORY OF IPSWICH MEDICINE

Mrs. I. HEWETT, librarian of the Ipswich Medical Library writes:

" The Ipswich Medical Library has decided to set up a historical section of records appertaining to the origin and growth of medicine in Ipswich and District, involving hospital practice, general practice, and public-health practice.

The historical section hopes to include documents, books, photographs, and instruments. Any help your readers can give would be appreciated and should be sent to the Ipswich Medical Library, Anglesea Road Wing, Ipswich and East Suffolk Hospital. "

GIFFEN HOUSE, ROYAL MEDICAL BENEVOLENT FUND

Commander J. G. HUNT, secretary of the Royal Medical Benevolent Fund, writes:

" May I draw the attention of the medical profession to Giffen House, 15, St. Simon's Avenue, Putney, which was opened in 1959 to provide five rent-and-rates-free unfurnished flats for retired married doctors with restricted incomes.

The house is situated in a quiet neighbourhood, not far from shops and public transport, and has a pleasant garden. The flats, of two rooms, kitchen and bathroom, with electric heating, are spacious and entirely self-contained. The only charge is a contribution to the maintenance of the property of £25 yearly.

We have two flats unoccupied. Applications and enquiries from retired married doctors are invited and should be addressed to: The Secretary, Royal Medical Benevolent Fund, 37, St. George's Road, Wimbledon, S.W.19."

Public Health

Clean Air

BY the end of last year, 510 smoke-control orders were in operation or preparation (compared with 226 at the end of 1958).[1] The orders covered 105,000 acres and 600,000 premises in England and Wales. Most of them related to " black areas ". Greater London had 140 orders, South-east Lancashire 84, the West Riding of Yorkshire 82, and the West Midlands 60.

1. Report of the Ministry of Housing and Local Government, 1959. H.M. Stationery Office. Cmnd. 1027. Pp. 229. 10*s*. 6*d*.

Parliament

Flame-resistant Materials

ON the adjournment on May 30 Mr. GEORGE CRADDOCK recalled that each year over 1500 people died and over 1 million were injured by fire. More than half of the hospital cases were due to accidents caused by wearing inflammable clothing, and most of the victims were children. A new and improved flame-resistant finish for materials had been developed by Proban Ltd. and could now be applied to cotton and winceyette. Yet mothers still had difficulty in obtaining non-inflammable material for nightdresses for their children. He asked the Minister to give Government backing to the labelling of safe materials, to enable shops which sell them to put up appropriate notices, and to arrange for the Board of Trade to help in advertising campaigns and to see that the testing of these materials was kept up to standard.

In his reply Mr. JOHN ROGERS, parliamentary secretary to the Board of Trade, said that the Molony Committee [1] in their interim report, which had now been presented to Parliament, had considered the suggestion that the use of flame-resistant fabrics should be a statutory requirement, at any rate in certain forms of cloth, such as children's nightwear. But they had been unable to recommend compulsion at this stage. To his knowledge, three processes could render certain fabrics flame-resistant. Large sums of money had been spent on their development. Materials treated by these processes had been handled by retailers but the public response was bitterly disappointing—" negligible " was the only word to describe it. Why was this so? They had been told that it was because the treatment made the cloth hard or harsh to the touch and because the treated fabrics were more expensive. It was claimed that a further technical development in at least one of the processes had now eliminated the adverse effect on handle. If so, there remained only the question of price. The processes added to the cost of, say, a nightgown for a small child about the price of 20 cigarettes. Was 4*s*. too much for safety?

There had been suggestions that taxpayers' money should be spent on an advertising campaign to persuade people to ask for fabrics which were either naturally flame-resistant or had been rendered so by one of the commercial processes. He did not think that this was a right purpose for the spending of the taxpayers' money, but he was attracted by the idea of a special campaign warning mothers of the dangers and appraising them of the availability of these new finishes and possibly new fibres which came on to the market. All were agreed that some educative and sustained publicity would be valuable. The only difference between them was whether this should be undertaken by the taxpayer or by those who ultimately hoped to profit by the exercise—namely, the makers of the fibres, the makers-up of the garments, and the distributors who sold the children's nightwear in the shops. For such a campaign to be effective it was essential that these garments should be stocked widely, and he would like to see the big retail stores give a lead by stocking flame-proof pyjamas and nightgowns. He believed that the stores and the makers-up should stress this feature in their advertisements continuously. We must hammer it home until it was accepted by the public that these fabrics were available in most of the shops throughout the length and breadth of the country. Nevertheless, he still thought that it was not something on which the Government ought to spend money.

Royal Assent

The Population (Statistics) Bill, the Radioactive Substances Bill, and the Royal College of Physicians of London Bill received the Royal Assent on June 2.

QUESTION TIME

Medical Auxiliaries

Lord FRASER OF LONSDALE asked the Government whether, having regard to the general satisfaction felt at the result of the Royal Commission on Doctors' Remuneration and the Government implementation of its recommendations, and having regard also to the new importance now being attached to medical auxiliaries, as evidenced by the passage through Parliament of the Professions Supplementary to Medicine Bill, they will now set up a Royal Commission or other appropriate body to inquire into the salaries and conditions of work of the professional persons covered by this Bill.—Viscount HAILSHAM replied: In the view of Her Majesty's Government, the special circumstances which led to the decision to set up the Royal Commission on Doctors' and Dentists' Remuneration have no application to the professions covered by the Professions Supplementary to Medicine Bill. The remuneration and conditions of service of members of the professions employed in the National Health Service are negotiated by the National Health Service Professional and Technical Whitley Councils A and B, and the Government consider that the normal opportunities for negotiation provided by this machinery are fully adequate for their purpose.

Lord FRASER OF LONSDALE: With respect, does not this look like one law for the doctors and another law for the supplementary workers, without whom the doctors would be powerless to do their jobs? Does my noble friend know that the supplementary workers are not satisfied with the Whitley Council, and will he reconsider the answer which he has given?—Lord TAYLOR: Before the noble Viscount replies, may I ask whether he is not aware that there are Whitley Councils for the doctors, but that fact did not stop the setting up of a Royal Commission for them? These professions are in an infinitely worse financial position than the doctors, and, while not subscribing completely to the noble Lord's observations about doctors and the supplementary professions, I would agree that the value of their work is very great and their remuneration very poor.—Viscount HAILSHAM: I cannot for an instant accept the proposition that because a Royal Commission is set up to discuss the remuneration in one profession, in all other cases of wage negotiations it is to be treated as a slight on the employees if a Royal Commission is not set up in that profession, too. That seems to me to be the wrong way of approaching the matter; and it would, in fact, be a counsel of despair in all wage negotiations. The circumstances which led to the appointment of the Royal Commission for doctors and dentists were that a fundamental disagreement had developed between the Government and the two professions about the basis on which the professions' remuneration in the health service ought to be determined. Complex questions had arisen, such as the precise meaning of what had been implied by Government acceptance in principle of the three Spens reports. According to the Royal Commission, the disputes which arose did " nothing to promote the smooth working of the National Health Service ". I should hardly think that a comparable situation had arisen in relation to the seven supplementary professions. Since October, 1959, the National Health Service salaries and sessional fees of six of the seven professions covered by the Bill have been increased by agreements freely arrived at on the appropriate Whitley Council. The salaries of the remaining class, the radiographers, were determined, in default of agreement, by an award of the Industrial Court, effective from Feb. 1, 1959. In all cases the increases were more than would have been justified by increases in the cost of living alone, and in some cases were very considerable.

Lord STONHAM: I am sure the noble and learned Viscount is absolutely right in rejecting the suggestion of a Royal Commission; but is he aware that these people are disgracefully underpaid, a fact which creates great difficulties in the running of hospitals? Whilst conceding all he says about the Whitley Councils, I would ask him whether he would have a word with his right honourable friend to see if something could be done. After all, the last increase for radiographers was in February last year, and they are surely entitled now to a further increase.—Viscount HAILSHAM: I think I must assume in all wage negotiations that the ordinary negotiating machinery should be used first.

1. Consumer Protection: interim report. Cmnd. 1011. H.M. Stationery Office, 1960. 1*s*.

Obituary

JOHN FARQUHAR FULTON

O.B.E. (Hon.), M.D., B.S. Harvard, M.A., D.Phil., D.Sc., D.Litt. Oxon., F.R.C.P.

Prof. John Fulton, neurophysiologist and historian and bibliographer of medicine and science, died at his home in New Haven, Connecticut, on May 29 at the age of 60.

He was the son of J. F. Fulton, an ophthalmologist of St. Paul, Minnesota. He graduated B.S. at Harvard University in 1921 and went as a Rhodes scholar to Magdalen College, Oxford, where he became a university demonstrator in physiology under Sherrington. He was befriended by Lady Osler and was given the run of Osler's library where the great *Bibliotheca Osleriana* was in the making.

In 1927 he returned to Harvard to take the M.D. degree and worked as an associate in neurosurgery under Harvey Cushing at the Peter Bent Brigham Hospital in Boston. Election to a fellowship at Magdalen brought him back to Oxford in 1928 to continue his neurophysiological researches in Sherrington's laboratory until he was appointed Sterling professor of physiology at Yale University in 1931.

His capacity for hard work soon placed his department in the forefront of neurophysiological research laboratories, and his infectiously enthusiastic and endearing personality attracted students and workers from all over the world. Important papers were published by him and his associates in a steady stream.

His paper with C. F. Jacobsen on the functions of the frontal lobes (1937), his William Withering lectures at Birmingham University (1948), and his Sherrington lectures at Liverpool (1952) helped to provide a neuroanatomical rationale for leucotomy operations; while his *Physiology of the Nervous System* (1938) has become a standard text. Other important contributions were his monographs on *Muscular contraction and the reflex control of movement* (1926) dating from his Oxford days, *The sign of Babinski: a study of the evolution of cortical dominance in primates* (1932), and papers on human and comparative studies of cortical and autonomic nervous system function and localisation.

Despite this great scientific output, Fulton managed to carry on his humanistic studies in the history and bibliography of medicine and science.

As early as 1930 in his *Selected Readings in the History of Physiology* he showed an extraordinary grasp of important trends, experiments, and discoveries in the development of knowledge of vital processes. In 1932 his *Bibliography of the Honourable Robert Boyle* was published by the Oxford Bibliographical Society, and he was correcting page proofs for a new edition when he died. It remains the classic example of that most useful art of scientific bibliography which not only lists books and other writings but also analyses their contents and evaluates their contribution and place in the historical scene. His bibliography of Richard Lower and John Mayow was written on the same lines. His biography of *Harvey Cushing* (1946) was a work of piety and art worthy to take its place with Cushing's own *Life of Sir William Osler* (1924).

During the late war Fulton turned his energies to aviation medicine, and his work for the war effort in this country was recognised by his appointment as honorary O.B.E. He also organised the evacuation of a large party of English children to the United States, and he and his wife generously undertook the education and maintenance of some.

In 1951 Fulton left the chair of physiology at Yale and became Sterling professor of the history of medicine in the same university. His department rapidly achieved world status, and his editorship of the *Journal of the History of Medicine and Allied Sciences* was also successful. Though he never forsook his neurophysiological interests and remained editor of the *Journal of Neurophysiology*, he gave more and more time to historical and bibliographical subjects, and he had the satisfaction of seeing the department he created, and the great Harvey Cushing-Arnold Klebs-John Fulton collection of historical medical and scientific books, incorporated within Yale University as the most important centre of medical and scientific history in the world.

Fulton travelled often and widely, all over the world, and wherever he went he was known and loved. He received many lectureships and honorary degrees, including awards in no fewer than eighteen countries. He valued above all else the D.LITT. which he received at Oxford in 1957. He was elected F.R.C.P. under the special bye-laws, and he was an honorary member of the historical section of the Royal Society of Medicine and an original member of the Osler Club of London.

The following tribute comes from a medical librarian:

"John Fulton was a life-enhancer; the world will be a less enjoyable place for the innumerable friends he has left. His incessant activity, though it cost him his life, never seemed to weary his spirit. He would go to the ends of the earth to meet a friend, to watch new work, or to seek a rare book. He loved the Renaissance with its gusto for both the highest and the merriest pleasures, and shared its urge towards new discoveries. He was a ransacker of book-shops but a generous friend to many libraries, not only the munificent co-founder of the splendid medical-historical collection at Yale. Last year he put on record his conviction that the recent growth of the medical library is 'challenging evidence of its importance in education and research'. Many, indeed most, medical librarians in America, Canada, and Britain can hardly count how much they owe to John's unfailing encouragement of their efforts."

R. A. H. writes:

"Fulton's was a manysided personality with apparently contrary characteristics making up a harmonious whole. To name only a few: he had an inexhaustible capacity for work and could relax and enjoy himself with equal vigour; he was as enthusiastic over a book on a shelf as over good food at a banquet; he was an untiring collector and yet so generous that libraries in many lands have reason to be grateful to him for gifts of rare books which he felt properly belonged to their collections; he was a public-spirited individualist not without a lovable streak of vanity who could devote himself equally to causes and persons; his views were carefully arrived at and firmly held, yet he was quick to accept and foster new ideas; he had the capacity to abstract himself completely when absorbed but was always ready to meet and exchange ideas with kindred minds; for him to commune with great figures of the past like William Harvey and Kenelm Digby was as lively as gossip about his own contemporaries, which he also enjoyed. He regarded all workers in the advancement of knowledge—whether scientific, historical, or bibliographical—as belonging to a club of which he was proud to be a member. In it he included the men of the past (hence his devotion to history) as well as the generation to come (hence his active and unstinting support for the young and aspiring). He caught at Oxford the scientific spirit of Sherrington and the humanistic tradition of Osler to whose library his widow gave him the key.

From both he learnt to stimulate others and in this he was uniquely successful."

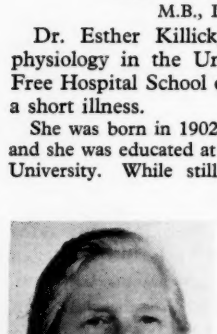
In 1923 Professor Fulton married Lucia Pickering Wheatland, who survives him.

ESTHER MARGARET KILLICK

M.B., D.Sc. Leeds, M.R.C.P.

Dr. Esther Killick, Sophia Jex-Blake professor of physiology in the University of London at the Royal Free Hospital School of Medicine, died on May 31 after a short illness.

She was born in 1902, the daughter of Dr. Arthur Killick, and she was educated at Leeds Girls' High School and Leeds University. While still a student she worked with May Mellanby at Sheffield, and their research on calcification in rabbits was published in the *Journal of Physiology* in 1926. After qualifying in 1928 Dr. Killick was appointed an investigator to the Safety in Mines Research Board and began to study the effect of resistance on respiration. In this work she was closely associated with J. S. Haldane, who at that time was physiologist to the board. A series of papers published between 1934 and 1937 reported her findings on the acclimatisation of man and of mice to low concentrations of carbon monoxide. She continued to study these problems when she went to Birmingham in 1935 as lecturer in industrial medicine and to London in 1939 as lecturer in applied physiology at the London School of Hygiene and Tropical Medicine.



In 1941 she was appointed to her present chair, and of her work there a member of her department writes:

"Professor Killick was a most able administrator and head of department. She was appointed to her chair at a time when the Medical School was evacuated to Exeter and the war made conditions of work unusual. In the years after the war more money became available, and the department was virtually doubled in space as well as staff. She supervised the planning and equipment of the new part of the department, and it is a testimony to her foresight that already the output of research has increased and that a number of postgraduate workers have been attracted to spend a year or more in the department. She took every unselfish opportunity to develop a department in which teaching and research would attain equal importance.

"She was intensely interested in the welfare of her students, of whom she had a precise and detailed knowledge which sometimes appeared surprising. She seemed to have an infinite capacity to listen to both staff and students and was never unapproachable except when busy with an experiment. Even then, if interrupted she would always lend an ear. Her great calmness and logic had an influence in private conversation as well as in committee.

"Her published research work had to suffer during the war, but in the last few years she had made considerable contributions to the study of carbon-monoxide poisoning and the methods of resuscitation. It is a very great pity that she was unable to complete some of the many projects that she had in view."

Outside her own school she served the University of London as a member of the Board of Preclinical Studies, and she was its representative on the Board of Faculty of Medicine. She was also a member of the Industrial Health Research Board.

In 1938 Dr. Killick married Prof. A. St. G. Huggett. There are two daughters of the marriage.

JOSEPH MONTAGU LEES

M.A., B.M. Oxon., D.M.R.

Dr. J. M. Lees, consultant radiologist to the Leeds A and B groups of hospitals and to the Ministry of Pensions Hospital at Chapel Allerton, died on March 17 at the age of 55.

He was educated at Rugby and New College, Oxford, and qualified from Guy's Hospital in 1929. He was a Beaney scholar and later gained a Commonwealth fellowship. Early in his career he showed an interest in electrotherapeutic work and was for a time in charge of the electrotherapeutic department of the Prince of Wales's Hospital, Tottenham. He took his D.M.R. in 1935, and joined the late Dr. George Cooper in a combined X-ray diagnostic and therapeutic practice in Leeds. He held a commission in the Territorials and during the late war he served with the R.A.M.C. as radiologist. In 1945 he returned to his practice in Leeds. With the introduction of the National Health Service in 1948 he was appointed a consultant radiologist.

The diversity of Dr. Lees' personality is affectionately recalled by a friend who writes: "José's high intelligence was linked with an impish sense of fun which enabled him to extract the essence of life in its widest and most liberal sense. His deep faith in the Anglican Church led him to take a real interest in ecclesiastical administration, and his friends included two bishops and many other clergy. He had an extraordinary foible for collecting and hoarding papers, pamphlets, and an incredible number of odds and ends 'which might come in useful' until the bulging attics and his study became uninhabitable. He ran a fleet of second-hand cars of all sizes, shapes, and ages and during his war service in West Africa drove a car resplendent with a thatched roof."

Dr. Lees leaves a widow and two daughters.

Diary of the Week

JUNE 12 TO 18

Monday, 13th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. Brian Ackner: Psychiatric Aspects of Termination of Pregnancy.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
6 P.M. Dr. Catherine Smith (St. Louis): Cytology of the Membranous Labyrinth.

Tuesday, 14th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Psychiatry*. Prof. G. Langfeldt (Oslo): Diagnosis and Prognosis of Schizophrenia.

ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Mr. Aleck Bourne: Troubles of the Menopause.

Wednesday, 15th

UNIVERSITY COLLEGE, Gower Street, W.C.1
5 P.M. Dr. H. Wirz (Basle): Mechanism of Urinary Concentration and Dilution.

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. P. D'Arcy Hart: The Tuberculin Reaction.

ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5.15 P.M. Dr. J. B. West: Pulmonary Function in Disease.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. Henry Haber: Recent Advances in Histopathology of the Skin.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Prof. W. Neubauer (Ljubljana): Role of B.C.G. in Tuberculosis Control.

Thursday, 16th

ROYAL SOCIETY, Burlington House, Piccadilly, W.1
4.30 P.M. Sir John Eccles: Nature of Central Inhibitory Action. (Ferrier lecture.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Dr. R. M. Mason: Spondylitis.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26, Portland Place, W.1
7.30 P.M. Sir Philip Manson-Bahr: Around the World in 35 Days.

Friday, 17th

INSTITUTE OF CARDIOLOGY
5 P.M. (1, Wimpole Street, W.1.) Sir Russell Brock: Surgical Treatment of Pulmonary Stenosis. (St. Cyres lecture.)

Births, Marriages, and Deaths

DEATHS

KILLICK.—On May 31, suddenly after a short illness, Esther Margaret Killick, D.SC., M.R.C.P., professor of physiology in the University of London at the Royal Free Hospital Medical School.

Notes and News

A MEDICAL ASSOCIATION OF AUSTRALIA

THE Australian Federal Council of the British Medical Association has decided to form an Australian Medical Association. B.M.A. branches in Australia are unanimously of the opinion that a Medical Association, separate from but affiliated to the B.M.A., should be set up. A subcommittee has been appointed to prepare a skeleton constitution for the new Association, to be considered at the next Federal Council meeting. A convention is then to be held so that all sections of the medical profession in Australia may be consulted.[1] In a letter Dr. S. Wand, chairman of council, conveyed the parent body's good wishes for the future; and in reply Dr. H. C. Colville, president of the Federal Council, said that the closest possible affiliation would be achieved which would bring about a permanent bond between members of the profession in the two countries.[2]

MANAGEMENT OF DISASTER

As senior administrative medical officer of the South East Metropolitan Regional Hospital Board, Dr. James Fairley last year produced a plan for accidents or disasters too large to be handled by any one hospital.[3] Such plans need to be tested; and the exercise "Cascade" was held last February to see how things would work out in practice.

For this purpose it was assumed that a large school (St. Olave's) near Guy's Hospital was the administrative block of a large works in which a serious explosion took place just as shifts were being changed. To make the exercise as realistic as possible, the various organisations concerned were not given beforehand the time, place, and details. No fewer than 170 members of the Casualties Union, and medical students from Guy's Hospital, served as "casualties".

Exercise "Cascade" was started by a 999 telephone call to London Ambulance Service Control Room, reporting a terrible explosion at St. Olave's with many casualties. This was passed on to the Fire Service and the Metropolitan Police, and to Guy's Hospital. The fire and police services sent out their control units, and Guy's, being the first hospital alerted, sent a senior medical officer, followed, on his instructions, by a mobile medical team. At the same time the Emergency Bed Service were informed and warned other general and special hospitals to be ready to receive casualties and to send more mobile teams if called on.

Within a few minutes the Fire Service (which in London is accepted as the focal point at an "incident"), the police, the ambulance service, and the senior medical officer with the mobile medical team had arrived at the site and had set up their control units close to one another.

In accordance with the plan, the heads of the services set about assessing the situation, and, while the senior medical officer was taking part in this and was devising a casualty evacuation plan with the senior ambulance representative present, many casualties were rapidly removed to Guy's Hospital by the first ambulances to arrive. Although the senior medical officer directed how many casualties should be taken to each hospital, in practice many of the injured got away "without the medical officer at the site being aware of which were the serious cases". Moreover, the clearance of casualties from the site was so speedy that the hospitals tended to be swamped. Two lessons from this exercise, therefore, were that the senior medical officer must, in conjunction with the ambulance service, plan the timing as well as the direction of the flow of casualties and that, so far as their movements can be controlled, all casualties should go through a casualty post near or at the ambulance loading-point. This latter arrangement would meet another difficulty experienced during the exercise, which was that, through inadequate labelling or patients getting away on their own, documentation was complete for only 54 out of 70 casualties received at one hospital. This would be desperately important in a real disaster—not only for casualties themselves but also for the peace of mind of relatives, who will perhaps be harrying the Central Casualty Bureau (set up by the Metropolitan Police) for information on what has happened to their loved ones. To feed this bureau with prompt and accurate detail the police sent a team to each hospital: but by using short-wave telephony, which reduced the "ether space" for other messages, they hampered communications with the hospitals.

Other lessons which were drawn from the morning's work were:

The control units of all services concerned must be very close together or even be parts of one headquarters; and the heads of services should confer frequently.

There should be a prearranged reporting procedure, and the heads of services should be made clearly recognisable by uniform or labelled clothing.

Hospitals should be kept informed of the number of casualties coming to them, and at each there should be direction of ambulances so as to avoid congestion.

Radio telephony is very apt to get "jammed": indeed it nearly defeated its purpose. It should not be used if communication can be maintained by some other means, such as the public telephones or motor-cyclists.

There was need for many stretcher-bearers at the site and at the hospitals. These might be obtained by calling on members of voluntary bodies and by enlisting the help of members of the public.

The women staff of mobile teams felt the cold badly, because the boiler suits they were wearing could not be put on over a uniform dress. These suits might be worn over slacks and a woollen jumper.

From the report of the discussion which followed, it is clear that exercise "Cascade" was a success—partly because it showed that the basic plan was sound, and partly because detection of the weak points should enable the arrangements to be improved.

1. *Med. J. Aust.* May 28, 1960, p. 864.
2. *ibid.* May 21, 1960, p. 817.
3. See *Lancet* 1959, i, 1278.

University of Birmingham

The title of professor of immunological pathology has been conferred on Dr. P. G. H. Gell, reader in experimental pathology.

Dr. Gell was born in 1914 and was educated at Stowe School. He studied at the University of Cambridge and at University College Hospital, London. After qualifying in 1939 he worked in the Emergency Public Health Laboratory Service and in 1943 he was seconded to work with Sir Charles Harington on sensitisation of the skin to chemical explosives in Ordnance factories. From 1945 to 1948 Dr. Gell was assistant to the director of the Bureau of International Standards at the National Institute for Medical Research. He took up his present appointment in 1948.

The Leonard Parsons lectures will be delivered in 1961 by Dr. Lawson Wilkins, associate professor of pediatrics in Johns Hopkins University.

University of Bristol

Dr. A. E. Read has been appointed lecturer in medicine.

University of Durham

Dr. A. G. Heppleston, senior lecturer in pathology at the Welsh National School of Medicine, Cardiff, has been appointed to the chair of pathology in the Newcastle division.

Dr. Heppleston graduated M.B. with honours from the University of Manchester in 1938 and became M.R.C.P. three years later. He held a Dorothy Temple Cross research fellowship and was medical chief assistant at Manchester Royal Infirmary before taking up his present appointment. He then proceeded to the degree of M.D. with commendation in 1954.

Royal College of Physicians of Edinburgh

To commemorate the visit of Queen Elizabeth, the Queen Mother, to the college last November, when she formally signed the roll as an honorary fellow, the honorary fellowship is being conferred on the following:

Lord Adrian, O.M., Sir John Boyd, Prof. Crighton Bramwell, Lieut.-General Wajid Ali Burki, Sir Howard Florey, Sir Harold Himsworth, Dr. Vasant Ramji Khanolkar, Viscount Malvern, C.H., Mr. R. G. Menzies, C.H., Dr. Wilder Penfield, O.M., Prof. E. G. Sayers, and Lord Strathclyde.

Royal College of Physicians of Ireland

At a meeting on June 3 the following were admitted to the fellowship:

J. D. Whiteside, Patricia M. Alston, Joan M. Mullaney.

M. B. Levine was admitted to the membership and the following to the licence and membership:

Joseph Alvey, Phelim Donnelly, J. B. Hourihane, C. F. McCarthy.

Royal College of Surgeons in Ireland

On June 1 the fellowship was conferred on Ratan Lal Agarwal.

Faculty of Anæsthetists.—The fellowship of the faculty has been awarded to the following:

T. J. Gilmartin, dean; V. O. McCormick, vice-dean; P. Drury Byrne, P. Nagle, S. Kenny, P. Murray, J. Woodcock, R. Davys, J. Dundee, S. Love, K. Bayne, W. Bingham, S. Bose, J. Boyd, J. D. Bourke, G. J. C. Brittain, A. B. Bull, F. M. Bryn, D. G. Coleman, W. S. Davis, J. B. Glynn, T. F. Heavey, J. C. Hewitt, A. H. Kasasian, O. V. S. Kok, M. V. Lemon, B. Lyne, P. R. Mersham, M. Murphy, J. MacAuley, M. O'Connor, S. D. Oliver, Lady Read, D. L. Scott, R. W. Shaw, M. A. Woods, Z. Lett.

The inaugural scientific meeting, which will take the form of a symposium on levels of anæsthesia, will be held in the college, St. Stephen's Green, Dublin, on Saturday, July 9, at 10 A.M. Further particulars may be had from the registrar of the college.

University College of Sierra Leone

Dr. Davidson Nicol, senior pathologist to the Government of Sierra Leone, has been appointed principal of the University College of Sierra Leone (Fourah Bay College).

He was born in Sierra Leone in 1924 and he was educated in West Africa, the University of Cambridge, and the London Hospital. He took first-class honours in part 2 of the natural sciences tripos in 1947, and qualified three years later. After holding resident appointments and a research assistantship in the department of physiology at the London Hospital, he became lecturer in physiology and biochemistry at Ibadan University College in Nigeria. He returned to Cambridge in 1954 with a Beit fellowship to work with Prof. F. G. Young and Dr. Fred Sanger in the department of biochemistry. He proceeded to the degrees of M.D. in 1956 and PH.D. in 1958 and was elected a fellow of Christ's College. He left Cambridge last year to join the Sierra Leone medical services. He is a member of the West African Medical Research Council and has published work on tropical malnutrition, the structure and biological activity of insulin peptides, and the tropical anæmias.

Society of Apothecaries of London

At recent examinations the following were successful:

M.M.S.A.—S. R. Hewitt, J. D. H. Mahoney, A. I. Qureshi, T. A. Rahman.

L.M.S.S.A.—A. K. Trounson, E. Aihie, L. B. Oshin, B. R. Collier, J. G. Fairer, C. G. D. Joseph, A. B. Chinnappa, O. Grundstrom, R. Handley, N. C. MacCallum, N. Sabokbar, L. A. B. Murray, G. Dickens, E. M. W. Haire, I. F. Ayad, W. G. S. Russell, J. L. Lane, Y. P. Lee, J. K. C. Chung.

Postgraduate Medical School of London

A symposium for consultants on the diagnosis and treatment of chronic forms of arthritis will be held on Sept. 22 and 23 at the school, Ducane Road, W.12. Further particulars will be found in our advertisement columns.

Rehabilitation: From Incapacity to Capacity

The British Council for Rehabilitation of the Disabled will hold a course and conference on this subject in Dublin, from July 12 to 14. Further particulars may be had from the council, Tavistock House South, London, W.C.1.

Institute of Child Health, London

Donations to the institute's building appeal fund now total £100,000 towards the target of £400,000. The Mathilda Marks Kennedy Trust have given £40,000 to provide the main lecture theatre in the new building.

Wellcome Trust

The Wellcome Trustees have made a grant of £50,000 (about $140,000) to the Massachusetts General Hospital, Boston, for the establishment of a Henry S. Wellcome research chair in medical science. The professor will be chosen by a special committee of the Massachusetts General Hospital, Harvard University, and the Massachusetts Institute of Technology, from a number of workers who have already achieved a high scientific reputation for their researches. The appointment will be made for ten years.

Royal Dental Hospital, London

Mr. Warwick James, F.R.C.S., has given £22,000 of 2½% Consolidated Stock to the School of Dental Surgery to endow a fund for research on dental anatomy.

British Medical Association

The Association is offering essay prizes for medical students, provisionally registered practitioners, members engaged in the practice of occupational health, and general practitioners. Awards are also to be made of the Middlemore and Katherine Bishop Harman prizes. Further particulars may be had from the secretary of the Association, Tavistock Square, London, W.C.1.

Birmingham's First Health Centre

On May 17 Mr. Derek Walker-Smith, the Minister of Health, opened a health centre in a new housing scheme at Nechells.

The centre, which is on the ground floor of a seven-storey block of flats, has six surgeries for general practitioners, a dental suite, a maternity and child-welfare centre, and a staff common-room. A reception office relieves the doctors of much of their clerical work. The office for the district home-help service is also in the centre, and a midwife and pupil occupy one of the flats above the centre. A resident caretaker takes messages after surgery hours. The centre is intended to serve 45,500 people and will cost £12,850 a year to run.

Eclampsia and Pre-eclampsia in Pregnancy

The International Society of Geographical Pathology is holding an international conference on this subject at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2, from June 28 to 30.

The president of the conference will be Prof. J. H. Dible and the speakers will include Dr. Ian MacGillivray, Dr. Richard Doll, Prof. J. C. McClure Browne, Sir Dugald Baird, Dr. A. D. T. Govan, Dr. H. B. Goodall, Dr. A. E. Claireaux, Dr. A. I. Klopper, Dr. M. J. R. Dawkins, Dr. J. V. Wigglesworth, Dr. D. A. Davey, Mr. M. Mahran, Dr. Edda Hanington, Dr. H. B. Perry, Dr. Heather J. Shelley, Prof. R. J. Kellar, Dr. H. G. Kohler, Dr. H. B. Goodall, Dr. W. E. Miall, and Dr. A. L. Cochrane.

Dr. L. Guttmann, director of the National Spinal Injuries Centre, Stoke Mandeville Hospital, Aylesbury, has received the 1960 international prize of the Spanish Association for Invalids and Handicapped.

The John Holt medal awarded to Sir Samuel Manuwa by the Liverpool School of Tropical Medicine was presented to him at Government House, Lagos, by the Governor-General of Nigeria, who read a congratulatory letter to Sir Samuel from the Duke of Edinburgh, patron of the school.

The Postgraduate Medical School heart surgery team (Mr. W. P. Cleland, Dr. D. G. Melrose, Mr. H. H. Bentall, and Dr. A. Holman) are carrying out a demonstration series of intracardiac surgical procedures, with the use of the extracorporeal circulation, in Helsinki, Finland.

The Anglo-German Medical Society is holding a symposium on medical education, on July 30 and 31, in Stuttgart. Further particulars may be had from the hon. secretary of the society, c/o department of chemical pathology, St. Mary's Hospital, London, W.2.

Appointments

BLYTH, R. A., M.B. Lpool: senior M.O. (mental health), Cheshire.

GORE, ELIZABETH, M.D., D.OBST., D.P.M.: consultant in child psychiatry, Harrogate child-guidance clinic of the West Riding Education Committee.

KAMALUDDIN, S. M., M.B. Calcutta, D.O.: assistant ophthalmologist, Barnsley area hospitals.

LE QUESNE, L. P., D.M. Oxon., F.R.C.S.: assistant consultant surgeon, Middlesex Hospital, London.

TURNER-WARWICK, R. T., D.M., B.SC. Oxon., F.R.C.S., M.R.C.P.: assistant consultant surgeon, Middlesex Hospital, London.

South-Western Regional Hospital Board:

FOSTER, G. S., M.D. Lond., M.R.C.O.G.: consultant obstetrician and gynæcologist, Weston-super-Mare group of hospitals.

GORDON, D. T., M.B. Aberd., D.P.H.: S.H.M.O. in infectious diseases, Scott Isolation Hospital, Plymouth.

PRYER, D. L., M.B. Lond., F.F.A. R.C.S.: consultant anæsthetist, Torbay area hospitals.

RODDIE, R. K., M.B. Belf., F.R.C.S.: consultant E.N.T. surgeon, Bristol clinical area hospitals.

SOLTAU, D. H. K., M.B. Cantab., F.R.C.S., M.R.C.O.G.: consultant obstetrician and gynæcologist, North Gloucestershire clinical area hospitals.

THOMSON, D. S., M.B. Durh., F.R.C.S.E., D.O.M.S.: consultant ophthalmic surgeon, North Gloucestershire clinical area hospitals.